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PHYSIOLOGICAL REVIEWS

VOL. IX JULY, 1929 No. 3

ORGANIZATION FOR PHYSIOLOGICAL HOMEOSTASIS

WALTER B. CANNON

The Laboratories of Physiology in the Harvard Medical School

Biologists have long been impressed by the ability of living beings to maintain their own stability. The idea that disease is cured by natural powers, by a *vis medicatrix naturae*, an idea which was held by Hippocrates, implies the existence of agencies ready to operate correctively when the normal state of the organism is upset. More precise modern references to self-regulatory arrangements are found in the writings of prominent physiologists. Pflüger (1877) recognized the natural adjustments leading toward the maintenance of a steady state of organisms when he laid down the dictum, "The cause of every need of a living being is also the cause of the satisfaction of the need." Similarly Fredericq (1885) declared, "The living being is an agency of such sort that each disturbing influence induces by itself the calling forth of compensatory activity to neutralize or repair the disturbance. The higher in the scale of living beings, the more numerous, the more perfect and the more complicated do these regulatory agencies become. They tend to free the organism completely from the unfavorable influences and changes occurring in the environment." Further, Richet (1900) emphasized the general phenomenon,—"The living being is stable. It must be in order not to be destroyed, dissolved or disintegrated by the colossal forces, often adverse, which surround it. By an apparent contradiction it maintains its stability only if it is excitable and capable of modifying itself according to external stimuli and adjusting its response to the stimulation. In a sense it is stable because it is modifiable—the slight instability is the necessary condition for the true stability of the organism."

To Claude Bernard (1878) belongs the credit of first giving to these general ideas a more precise analysis. He pointed out that in animals with complex organization the living parts exist in the fluids which bathe them, i.e., in the blood and lymph, which constitute the "milieu interne"

or "intérieur"—the internal environment, or what we may call the *fluid matrix* of the body. This fluid matrix is made and controlled by the organism itself. And as organisms become more independent, more free from changes in the outer world, they do so by preserving uniform their own inner world in spite of shifts of outer circumstances. "It is the fixity of the 'milieu intérieur' which is the condition of free and independent life," wrote Bernard (1878, i, pp. 113 and 121), "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment." "No more pregnant sentence," in Haldane's (1922) opinion, "was ever framed by a physiologist."

DEFINITION OF HOMEOSTASIS. The general concept suggested in the foregoing quotations may be summarized as follows. The highly developed living being is an open system having many relations to its surroundings—in the respiratory and alimentary tracts and through surface receptors, neuromuscular organs and bony levers. Changes in the surroundings excite reactions in this system, or affect it directly, so that internal disturbances of the system are produced. Such disturbances are normally kept within narrow limits, because automatic adjustments within the system are brought into action, and thereby wide oscillations are prevented and the internal conditions are held fairly constant. The term "equilibrium" might be used to designate these constant conditions. That term, however, has come to have exact meaning as applied to relatively simple physico-chemical states in closed systems where known forces are balanced. In an exhaustive monograph L. J. Henderson (1928) has recently treated the blood from this point of view, i.e., he has defined, in relation to circumstances which affect the blood, the nice arrangements within the blood itself, which operate to keep its respiratory functions stable. Besides these arrangements, however, is the integrated coöperation of a wide range of organs—brain and nerves, heart, lungs, kidneys, spleen—which are promptly brought into action when conditions arise which might alter the blood in its respiratory services. The present discussion is concerned with the physiological rather than the physical arrangements for attaining constancy. The coördinated physiological reactions which maintain most of the steady states in the body are so complex, and are so peculiar to the living organism, that it has been suggested (Cannon, 1926) that a specific designation for these states be employed—*homeostasis*.

Objection might be offered to the use of the term *stasis*, as implying something set and immobile, a stagnation. Stasis means, however,

not only that, but also a condition; it is in this sense that the term is employed. *Homeo,* the abbreviated form of *homoio,* is prefixed instead of *homo,* because the former indicates "like" or "similar" and admits some variation, whereas the latter, meaning the "same," indicates a fixed and rigid constancy. As in the branch of mechanics called "statics," the central concept is that of a steady state produced by the action of forces; *homeostatics* might therefore be regarded as preferable to homeostasis. The factors which operate in the body to maintain uniformity are often so peculiarly physiological that any hint of immediate explanation in terms of relatively simple mechanics seems misleading. For these various reasons the term homeostasis was selected. Of course, the adjectival form, *homeostatic,* would apply to the physiological reactions or agencies or to the circumstances which relate to steady states in the organism.

CLASSIFICATION OF HOMEOSTATIC CONDITIONS. According to Bernard (1878, ii, p. 7), the conditions which must be maintained constant in the fluid matrix of the body in order to favor freedom from external limitations are water, oxygen, temperature and nutriment (including salts, fat and sugar).

Naturally during the past fifty years new insight has been acquired and therefore a more ample classification than that just given should be possible. Any classification offered now, however, will probably be found to be incomplete; other materials and environmental states, whose homeostasis is essentially important for optimal activity of the organisms, are likely to be discovered in the future. Moreover, in any classification there will be cross-relations among the homeostatic states; a uniform osmotic pressure in the body fluids, for example, is dependent on constancy within them of the proportions of water, salts and protein. The classification suggested below, therefore, should not be regarded as more than a serviceable grouping of homeostatic categories; it may claim only the merit of having served as a basis for studying the means by which the organism achieves stability:

A. Material supplies for cellular needs.
   1. Material serving for the exhibition of energy, and for growth and repair—glucose, protein, fat.
   2. Water.
   3. Sodium chloride and other inorganic constituents except calcium.
   4. Calcium.
   5. Oxygen.
   6. Internal secretions having general and continuous effects.

B. Environmental factors affecting cellular activity.
   1. Osmotic pressure.
   2. Temperature.
   3. Hydrogen-ion concentration.

Each item in the foregoing list exists in a relatively uniform condition of the fluid matrix in which the living cells of the organism exist. There are variations of these conditions, but normally the variations are within narrow limits. If these limits are exceeded serious consequences may result or there may be losses from the body. A few examples will make clear these relations:

A reduction of the glucose in the blood to about 70 mgm. per cent (e.g., by insulin) induces the "hypoglycemic reaction" (Fletcher and Campbell, 1922), and a reduction below 45 mgm. per cent brings on convulsions and possibly coma and death; an increase of the percentage above 170 to 180 mgm. results in loss via the kidneys. Too much water in the body fluids results in "water intoxication," characterized by headache, nausea, dizziness, asthenia, incoördination (Rowntree, 1922); on the other hand, too little water results in lessened blood volume, greater viscosity, and the appearance of fever (Keith, 1922; Crandall, 1899). Sodium (with the attendant chloride ion) is especially important in maintaining constant the osmotic properties of the plasma; if the percentage concentration rises from 0.3 to 0.6 per cent, water is drawn from the lymph and cells, and fever may result (Freund, 1913; Cushny, 1926, p. 19); on the other hand, if the concentration is reduced, toxic symptoms appear—marked reflex irritability, followed by weakness, shivering, paresis and death (see Grünwald, 1909). The normal level of calcium in the blood is about 10 mgm. per cent; if it falls to half that concentration, twitchings and convulsions are likely to occur (MacCallum and Voegtlin, 1909); if it rises to twice that concentration, profound changes take place in the blood, which may cause death (Collip, 1926). The normal daily variations of body temperature in man range between 36.3°C. and 37.3°C.; though it may fall to 24°C. and not be fatal (Reincke, 1875), that level is much lower than is compatible with activity; and if the temperature persists at 42–43°C., it is dangerous because of the coagulation of certain proteins in nerve cells (Halliburton, 1904). The hydrogen-ion concentration of the blood may vary between approximately pH 6.95 and pH 7.7; at a pH of about 6.95 the blood becomes so acid that coma and death result (Hasselbalch and Lundsgaard, 1912); above pH 7.7 it becomes so alkaline that tetany appears (Grant and Goldman, 1920). The heart rate (of the dog) has

been seen to decrease from 75 beats per minute to 50 when the pH fell from 7.4 to 7.0; and to increase from 30 per minute to about 85 when the pH rose from 7.0 to 7.8 (Andrus and Carter, 1924). The foregoing instances illustrate the importance of homeostasis in the body fluids. Ordinarily the shifts away from the mean position do not reach extremes which impair the activities of the organism or endanger its existence. Before those extremes are reached agencies are automatically called into service which act to bring back towards the mean position the disturbed state. The interest now turns to an enquiry into the character of these agencies.

An inductive unfolding of the devices employed in maintaining homeostatic conditions—an examination of each of the conditions with the object of learning how it is kept constant—would require more space than is permitted here. It will be possible, however, to define in broad terms the agencies of homeostasis and to illustrate the operation of some of those agencies by reference to the specific cases. Thus the account may be much abbreviated.

Two general types of homeostatic regulation can be distinguished dependent on whether the steady state involves *supplies* or *processes*.

HOMEOSTASIS BY REGULATING SUPPLIES. The characteristic feature of the homeostasis of supplies is provision for *A*, storage as a means of adjustment between occasional abundance and later privation and need, and for *B*, overflow or discharge from the body when there is intolerable excess. Two types of storage can be distinguished: a temporary flooding of interstices of areolar tissue by the plenteously ingested material, which may be designated *storage by inundation*; and an inclusion of the material in cells or in other relatively fixed and permanent structures—*storage by segregation*. We shall consider illustrations of these two types.

STORAGE BY INUNDATION. The analogy implied in this phrase is that of a bog or swamp into which water soaks when the supply is bountiful and from which the water seeps back into the distributing system when the supply is meager. There appears to be such an arrangement in the loose areolar connective tissue found under the skin and around and between muscles and muscle bundles, and also in other parts of the body. Connective tissue is distinguished from other kinds in being richest in extracellular colloid, in having a close relation to blood vessels—indeed, it serves as a support for the blood vessels—and in exposing an enormous surface area. In such structures chiefly do the agencies rule which hold not only mobile water but also substances

dissolved in it, i.e., electrolytes and glucose. Here there are few cells, but instead "a spongy cobweb of delicate filaments," each of which is composed of minute fibrils bound together by a small amount of "cement substance" (Lewis and Bremer, 1927). Within the fine mesh of these collagenous fibres occur mucoid and small amounts of albumin and globulin. In this mesh and bound by it in some manner water and its dissolved substances appear to be held. Probably the proportions of stored water, electrolytes and glucose do not vary beyond a fairly limited range. Because there is evidence, however, that water and electrolytes, at least, may be affected somewhat independently with regard to their retention and elimination, they will be considered separately.

Water. The evidence for water storage is best demonstrated in experiments which withdraw water from its reservoirs and which permit an examination of the amount held in them. After hemorrhage all tissues lose water. By comparing one side of the body with the other in the same animal (the cat) Skelton (1927) found that most of the water which leaves the tissues after bleeding comes from the muscles and the skin—i.e., where loose areolar tissue is most abundant; the amount per 100 grams of tissue, however, is much less from the muscles than from the skin. The observations by Engels (1904) on dogs are in harmony with those of Skelton. Engels found that though 48 per cent of the total body water is in muscles, as might be expected from the great bulk of muscle tissue, about 12 per cent is in the skin, nearly half again as much as is in the fluid blood. And after injecting 0.6–0.9 per cent sodium chloride solution into a vein for an hour, he discovered that 690 grams had been retained and that the muscles and the skin had taken up the solution to almost the same per cent.

That the water stored in the tissues passes out from them as it is needed is shown by the studies of Wettendorf (1901) on the state of the blood during water deprivation. His dogs were, of course, continually losing water through respiratory surfaces and kidneys. Yet one of his animals thirsted for 3 days with no change in the freezing point of the blood, and another for 4 days with a depression of only 0.01°C. Clearly this constancy must be due to the seepage of water from the reservoirs to the blood as fast as it is lost from the body.

Just how the water is brought to the reservoirs, how it is held there, and how it is released as required for preserving the osmotic homeostasis of the blood, is not yet satisfactorily explained. Doubtless a change in the balance between filtration pressure through the capillary walls and

osmotic pressure of the proteins, as expounded by Starling (1909), plays an important rôle. And naturally, conditions affecting the capillary wall (e.g., increasing its permeability), raising or lowering intracapillary blood pressure, or altering the concentration of the plasma proteins would affect the water content of the tissues. Diffusion pressure would likewise take part in the complex of active factors. Furthermore, as Adolph (1921) and Baird and Haldane (1922) have shown, the taking of sodium chloride can markedly influence the retention of water in the body. Probably other electrolytes likewise play a rôle. There is evidence also that the H- and OH-ion concentration may be important—a shift towards an alkaline reaction causing imbibition of water by connective tissue and an opposite shift resulting in release (Schade, 1925). That the thyroid gland is a determinative agent is indicated by the great increase of protein in the plasma and of albumin in the tissues in myxedema, and the disappearance of these conditions, together with a large release of water and sodium chloride, when thyroxin is administered (see Thompson, 1926). How these various factors coöperate when water and sodium chloride are needed in the circulation—after hemorrhage, for example—is not clear, and urgently calls for investigation. Krogh (1922) has written concerning the arrangement of water mobilization, "The nature of such a mechanism is entirely unknown and I should not like to venture even a guess regarding it"—and yet it is of primary significance for the organism.

Sodium chloride. There is good evidence that the sodium and chloride ions in the plasma may vary independently, and that of the two the base is much the more constant element (see Gamble and Ross, 1925; Gamble and McIver, 1925, 1928). In a study of steady conditions in the fluid matrix, therefore, the emphasis might properly be laid on the homeostasis of the fixed base. Since most of the facts now available, however, have come from experiments in which the behavior of sodium chloride has been examined, the present treatment of the subject must be concerned with that salt. The evidence for storage of sodium chloride in the body is found in retention under different conditions. With a fairly constant chloride intake abundant sweating and attendant loss of chloride through the skin are accompanied by a great reduction of the chloride output in the urine—a condition which continues although thereafter a diet rich in salt is taken; by this method of study a compensatory retention of 10 to 14 grams of sodium chloride has been observed (Cohnheim, Kreglinger, and Kreglinger, 1909). Further, the taking of concentrated sodium chloride by mouth results in the appear-

ance in the urine of only a part of the amount ingested—most of it is retained in storage in the body; and even if thereupon enough water is drunk to produce a diuresis the urine has a low salt content, i.e., the salt is not given up readily from its storage place (Baird and Haldane, 1922).

When a search is made for the sodium chloride reserve in the body the highest percentage of chloride is found in the skin and the lowest in the muscles—indeed, on a chloride-rich diet one-third of the chloride of the body may be in the skin, and after an intravenous infusion of a sodium-chloride solution the skin may hold the stored chloride to an amount varying in different experiments between 28 and 77 per cent of the amount injected. This evidence is supported by observations on animals fed a chloride-poor diet. Under these circumstances between one and two-tenths of the chloride content of the body is lost, and of this amount between 60 and 90 per cent comes from the skin, though the skin is only 16 per cent of the total body weight (Padtberg, 1910). It is noteworthy that the blood gives up relatively little of its chloride content; again the circulating fluid is kept constant by supplies from tissue storage.

It is well to recognize that the way in which sodium chloride is held in the skin, whether by adsorption on surfaces in areolar tissue or by solution in the interstitial fluid of the areolar spaces, is not known. Probably it is osmotically inactive. That sodium chloride and water are closely related in storage, however, seems to be well established (see Adolph, 1921).

Glucose. The first, temporary depository for excessive blood sugar, as for excessive sodium chloride, is the skin. When sugar or other readily digestible carbohydrate is a large constituent of the diet the glycemic concentration rises commonly from about 100 to 170 mgm. per cent (Hansen, 1923). During this period of high percentage of sugar in the blood there is also a high percentage in the skin (Folin, Trimble and Newman, 1927). This appears to be again an example of storage by inundation. No chemical change occurs in the sugar. No special device is required either to deposit it in the temporary reservoir or to remove it therefrom. As the circulating sugar is utilized or placed in more permanent storage in the liver and in muscle cells, the glycemic level falls. Thereupon the more concentrated glucose, which has overflowed into the spaces of the skin and possibly into other regions where alveolar tissue is abundant, gradually runs back into the blood again and then follows the usual courses of the blood glucose into use or into the fixed reserves.

STORAGE BY SEGREGATION. As previously stated, this mode of storage, commonly within cells, is stable and lasting. It is seen, for example, in carbohydrate reserves as glycogen, in protein reserves as irregular masses in liver cells, in fat reserves as adipose tissue, and in calcium reserves as the trabeculae of the long bones. It differs from storage by inundation in being subject to much more complicated control. Storage by inundation may be regarded as a process of outflow from the blood stream and backflow into it according to the degree of abundance—a relatively simple process. Storage by segregation commonly involves changes of physical state or of molecular configuration and appears to be subject to nervous or neuro-endocrine government. This rather tentative statement is used because of the large gaps in our knowledge, which further consideration will reveal. We shall consider the segregated storage of carbohydrate, protein, fat and calcium.

Carbohydrate. The best example of homeostasis by means of segregation is offered by the arrangements for storage and release of carbohydrate. As is well known, when carbohydrate food is plentiful the glycogen reserves in the liver are large; in prolonged muscular work these reserves may be almost wholly discharged (Kulz, 1880); and yet, while they are being discharged, the blood sugar is maintained at concentrations which neither result in the possibility of sugar loss through the kidneys, nor in the possibility of disturbance from hypoglycemia (Campos, Cannon, Lundin and Walker, 1929). A mechanism must exist, therefore, to release sugar from the liver as it is needed.

An insight into the action of factors which prevent the fall of the blood sugar to a seriously low level may be obtained by a study of the effects of insulin. As stated above, the reduction of the glycemic concentration to about 70 mgm. per 100 cc. by insulin induces the "hypoglycemic reaction," characterized by pallor, rapid pulse, dilated pupils and profuse sweating. These are signs of sympathetic innervation. That this is part of a general display of activity by the sympathetic division of the autonomic system is shown by the involvement of the adrenal medulla. Using the denervated heart as an indicator, Cannon, McIver and Bliss (1923, 1924) found that as the blood sugar fell a critical point was reached at about 70 mgm. per cent, when the heart began to beat faster—a phenomenon which failed to appear if the adrenal glands had been inactivated. If the blood sugar continued to fall the heart rate became faster, thus indicating a greater output of adrenin; and if the blood sugar rose, either because of intravenous injection of

glucose or because of a physiological reaction, the heart beat returned to its original slow rate, thus indicating a subsidence of the extra discharge of adrenin. Since medulliadrenal secretion is controlled by splanchnic impulses, and since such impulses in coöperation with secreted adrenin are highly effective in causing an increase of blood sugar (Bulatao and Cannon, 1925; Britton, 1928), it is clear that the reduction of the glycemic percentage below a critical level calls forth an agency—the sympathico-adrenal system—to correct the condition. These observations have been confirmed by Abe (1924) who used the denervated iris to signal a greater output of adrenin, and by Houssay, Lewis and Molinelli (1924) who used for that purpose an adrenal-jugular anastomosis between two dogs. If, in spite of the increasingly active service of this agency as the blood sugar falls, the fall is not checked, convulsions occur (at about 45 mgm. per cent) and each convulsion is associated with a maximal display of sympathico-adrenal activity. If the liver is well supplied with glycogen such activity can restore the blood sugar to the normal level and thus abolish the conditions which brought on the convulsive attacks (McCormick, Macleod, Noble and O'Brien, 1923).

The importance of this agency has been demonstrated by experiments on healthy non-anesthetized animals in which the adrenal glands had been inactivated. The fall of blood sugar after insulin was less retarded at the critical level in cats thus altered, and the convulsive seizures were induced sooner and with smaller doses than in animals with active glands (Cannon, McIver and Bliss, 1924). This increased sensitiveness to insulin after medulliadrenal inactivation has also been proved true of rats (Lewis, 1923), of rabbits (Sundberg, 1923) and of dogs (Lewis and Magenta, 1925; Hallion and Gayet, 1925). The evidence that a small dose of insulin, mildly effective in a normal animal, causes in an animal treated with ergotamine profound hypoglycemia, with convulsions and collapse (Burn, 1923), is in harmony with this testimony, for the drug, though without influence on the action of insulin, paralyzes the protective sympathico-adrenal mechanism. Section of the splanchnic nerves, according to Lewis and Magenta, renders animals more sensitive than does removal of one adrenal and denervation of the other by splanchnic section; under the latter circumstances, it should be noted, one splanchnic is still innervating the liver.

Operation of agencies opposed to those just considered occurs when the blood sugar tends to rise. The efficacy of these agencies is revealed when an excess of glucose is ingested. The blood sugar rises to a level

close to that at which it escapes through the kidneys, but normally it does not often surpass that level (Hansen, 1923). The excess sugar, apart from that set aside by inundation, is either stored in the liver or in muscles, or is converted to fat, or is promptly utilized. There is evidence that the process of storage by segregation in hepatic and muscle cells is dependent on secretion of insulin: 1. Removal of the pancreas results in prompt appearance of hyperglycemia and a great reduction of the hepatic glycogen reserves. 2 .The administration of insulin to sugar-fed *depancreatized* dogs reduces the blood sugar to the normal percentage and causes glycogen to accumulate again in large amounts in the liver (Banting, Best, Collip and Noble, 1922). 3. Insulin in small doses causes a deposit of glycogen in the liver of phlorizinized rabbits and cats, even though no sugar is provided (Cori, 1925). 4. Insulin injected into decapitated, eviscerated cats causes a decided increase in the glycogen deposit in the muscles, especially when extra blood sugar is provided (Best, Hoet and Marks, 1926). 5. Islet cells in a remnant of the pancreas degenerate, showing signs of overwork (Allen, 1920; Homans, 1914), when carbohydrate is fed; from this evidence it appears that hyperglycemia stimulates the islet cells to secrete. This stimulation may be direct, as proved by absence of diabetes if a portion of the pancreas is transplanted under the skin and the rest of the gland is then removed and by the appearance of the disease when the engrafted piece is extirpated (Minkowski, 1908), by prompt reduction of hyperglycemia from injected glucose although the vagi have been severed (Banting and Gairns, 1924), or by reduction of diabetic hyperglycemia when a pancreas is connected with blood vessels in the neck (Gayet and Guillaumie, 1928). There is evidence also of a nerve control of insulin secretion, for stimulation of the right vagus reduces blood sugar, but not if the vessels of the pancreas are tied (Britton, 1925); and, according to Zunz and La Barre (1927), after union of the pancreatic vein of dog A to the jugular of dog B injection of glucose into A causes the blood sugar to fall in B—an effect that does not occur if the vagi of A have been cut or atropine given. That this nervous control is not necessary does not prove that it is useless when present—for example, the heart after denervation will continue beating and will maintain the circulation! It may be that the vagus provides a fine adjustment for insulin secretion as the sympathetic does for secretion of adrenin.

The general scheme which has been presented above is represented diagrammatically in figure 1. As Hansen (1923) has pointed out, there are normal oscillations in blood sugar occurring within a relatively

narrow range. Possibly these ups and downs result from action of the opposing factors, depressing or elevating the glycemic level. If known elevating agencies (normally and primarily the sympathico-adrenal apparatus) are unable to bring forth sugar from storage in the liver, the glycemic level falls from about 70 to about 45 mgm. per cent, whereupon serious symptoms (convulsions and coma) may supervene. The range between 70 and 45 mgm. per cent may be regarded as the *margin of safety*. On the other hand, if the depressing agency (the insular or vago-

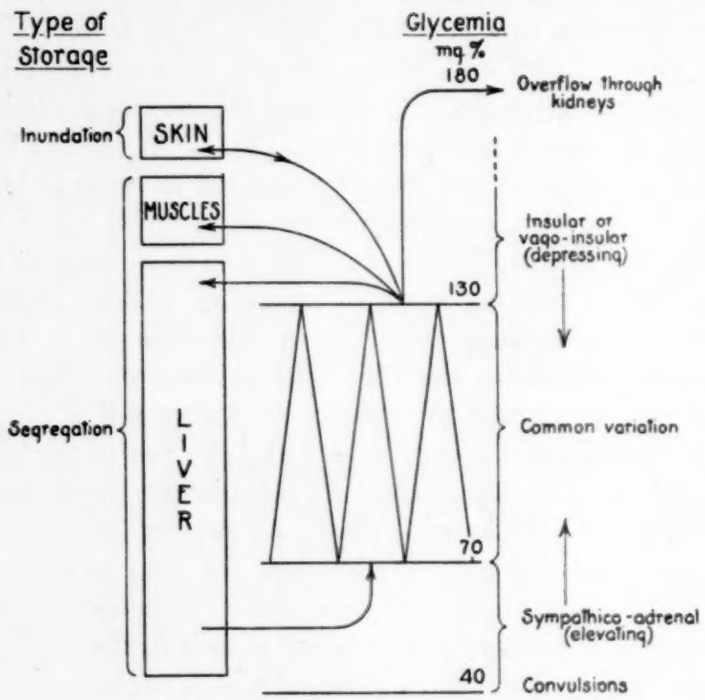

Fig. 1

insular apparatus) is ineffective, the glycemic level rises to about 180 mgm. per cent and then sugar begins to be lost through the kidneys. The range from 100 or 120 to 180 mgm. per cent may be regarded as the *margin of economy*—beyond that, homeostasis is dependent on wasting the energy contained in the sugar and the energy possibly employed by the body to bring it as glucose into the blood.[1]

[1] Evidence opposed to the foregoing views has been brought forward recently by Cori and Cori (1928). They state that "the most prominent effect of epinephrin is observed in the peripheral tissues and consists in a mobilization of muscle glycogen and in a decreased utilization of blood sugar"; and that insulin causes a rapid disappearance of the hepatic stores, due to increased use of blood

Protein. The homeostasis of protein is perhaps widely manifested in the constancy of body structure. That would include the blood, however, and since we are concerned with the conditions which keep uniform the fluid matrix of the body, we shall pay particular attention only to that.

The importance of constancy of the plasma proteins need not be

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sugar in peripheral tissues and to "compensatory mobilization of liver glycogen." These declarations, so contrary to evidence long accepted, call for comment. First, they gave doses of adrenalin (0.2 mgm. per k.) and of insulin (7.5 units per k.) far beyond physiological limits (equivalent to 14 cc. of adrenin and 525 units of insulin in a man of 70 k.!). Pronounced physiological effects have been obtained in white rats (which they used) with a dose of adrenin *one-twentieth* of their dose. Although they argue that their adrenin doses were slowly and fairly evenly absorbed, they present no actual evidence; and the fact that the highest blood sugar in their experiments came early and was associated with the lowest glycosuria indicates both that their argument is ill-based and that the huge doses disturbed the circulation. Further, "mobilization of muscle glycogen" consists, they explain, in a change of the glycogen to lactic acid, and from this circulating lactic acid a reconstruction of glycogen by the liver. But the glycogen in muscle is there for use; to "mobilize" it without use is like withdrawing forces from the firing line and settling them in barracks! Again, in declaring that adrenin causes hyperglycemia "because the utilization of blood sugar is diminished" they neglect the evidence: 1, that intravenous injection of adrenin raises blood sugar with almost no latent period (Tatum, 1921); 2, that emotional excitement can raise blood sugar 30 per cent or more in a few minutes, but not after adrenalectomy (Britton, 1928), and that the same phenomena are seen when the splanchnics are stimulated (Macleod, 1913), and 3, that after an adrenin injection the blood sugar rises quickly in the liver veins and only later is equaled in the portal or femoral vein (Vosburgh and Richards, 1903)—all evidence against their views, because the hyperglycemia comes too soon and is too clearly of hepatic origin to be ascribed to failure of use of glucose by peripheral tissues. Moreover, their belief that adrenin causes "decreased utilization of blood sugar" is contradicted by the observation that when glucose and adrenin are supplied to the heart-lung preparation sugar consumption rises to about four times the former amount (Patterson and Starling, 1913), and that dogs exhausted by running can be made to continue (i.e., using sugar in their muscles) and will put forth from 17 to 44 per cent additional energy if they are given subcutaneously small doses of adrenin (0.02–0.04 mgm. per k., sometimes repeated) but not if a large dose (0.17 mgm. per k.—n.b., *less* than that used by the Coris) is given (Campos, Cannon, Lundin and Walker, 1929). Finally, although they mention a "compensatory mobilization of liver glycogen" as the cause of depleted hepatic stores after their enormous doses of insulin, they do not hint at the nature of the compensatory process, though they report low blood-sugar levels which would set in action the sympathico-adrenal apparatus. For these various reasons the views advanced by Cori and Cori seem not to warrant a surrender of the well established conceptions of the action of adrenin and insulin.

emphasized. Because they exert osmotic pressure and do not ordinarily escape through capillary walls, they prevent the salts dissolved in the blood from passing freely into perivascular spaces and out from the body through the renal glomeruli (Starling, 1909). When Barcroft and Straub (1910) removed much of the blood from a rabbit, separated the corpuscles, and reinjected them suspended in an equal volume of Ringer's solution instead of plasma, so that the difference was merely a reduction of the colloid, urine secretion was increased *forty times*. The development of "shock"—engorgement of liver, spleen, kidneys, intestinal mucosa and lungs, with accumulation of fluid in the intestine—noted by Whipple, Smith and Belt (1920) when the plasma proteins were reduced to 1 per cent, tells the same story. But not only does homeostasis of the plasma proteins provide for homeostasis of the blood volume; at least one of them (fibrinogen) is, in case of hemorrhage, essential for preservation of the blood itself. The very existence of the fluid matrix of the body is dependent, therefore, on constancy of the proteins in the plasma—and usually they are remarkably constant in various conditions of health and disease.

Blood is the one tissue in the body from which protein can be quantitatively removed and its restoration then studied. When by plasmapharesis the plasma proteins are reduced from about 6 to about 2 per cent there is a prompt rise in their concentration within fifteen minutes, a more gradual restoration thereafter during the first twenty-four hours to about 40 per cent, and full recovery in two to seven days. It may be that the prompt rise is relative, due to escape of salt solution from the blood vessels, although arguments have been advanced that it results from emergency discharge of the proteins from storage (Kerr, Hurwitz and Whipple, 1918). The slower recovery seems certainly dependent on the liver, for the following reasons: 1. If the liver has been injured by phosphorus or chloroform, restoration of the plasma proteins is delayed. 2. Dogs with an Eck fistula may have no restoration for the first three days after plasmapharesis. And 3, fibrinogen, which usually is completely restored within twenty-four hours, is not thus restored if the liver is unable to act (Foster and Whipple, 1922; Meek, 1912).

The evidence that the liver is important for homeostasis of proteins in the blood plasma raises the question whether protein is stored there. Results obtained by histological and biochemical methods have agreed in supporting the conclusion that hepatic cells can carry reserve protein as well as reserve carbohydrate. The early observations of Afanassiew

(1883) that the liver cells of dogs given an abundance of "albuminates" increase in size and contain protein granules between the structural strands, have been confirmed by Berg (1914, 1922), by Cahn-Bronner (1914), by Stübel (1920) and by Noël (1923). In sum, these recent histological studies show that when animals are fed protein there appear in the hepatic cells fine droplets or masses, which react to Millon's reagent, which yield the ninhydrin reaction of a simple protein, which disappear on fasting, and which reappear on feeding protein or amino acids. The biochemical analyses by Seitz (1906), who found that in fed animals the total nitrogen of the liver in relation to that in the rest of the body is from two to three times as great as in fasting animals, have been supported by the results obtained by Tichmeneff (1914). He starved mice for two days, then killed half of them and after giving the others an abundance of cooked meat killed them and compared the livers of the two groups. Expressed in percentage of body weight, the livers of the meat-fed animals increased about 20 per cent, with the hepatic nitrogen content augmented between 53 and 78 per cent.

Although the experiments on homeostasis of plasma proteins indicate that the liver is an important source of these materials in case of need, and although the testimony cited above would justify consideration of the liver as a storage place for protein, the modes of storage and release are almost wholly unknown. Stübel (1920) did, indeed, observe that the small protein droplets or masses in the hepatic cells could be greatly reduced by injecting adrenin subcutaneously. If these masses help to supply essential protein elements for blood clotting, as the dependence of fibrinogen on the liver would imply, their liberation by adrenin and by conditions which would excite the sympathico-adrenal apparatus might account for certain phenomena of faster clotting. Coagulation is more rapid after adrenin injections (see Cannon and Gray, 1914; La Barre, 1925; Hirayama, 1925), after splanchnic stimulation (Cannon and Mendenhall, 1914), or after large hemorrhage which calls the sympathetic into action (Gray and Lunt, 1914), but only if the blood is allowed to flow through the liver and intestines. In this category also is the very rapid clotting of blood taken at the height of the hypoglycemic reaction (Macleod, 1924), when sympathico-adrenal activity is maximal.

It is quite possible that protein is stored in other places than the liver, and also that the thyroid gland is an important agency for controlling both storage and release. Boothby, Sandiford and Slosse (1925) have reported that with a uniform nitrogen intake a negative nitrogen balance

exists while thyroxin is establishing a new higher metabolic level. After its establishment there is a smaller deposit of nitrogen in the body. Now if thyroid dosage is stopped (while the uniform nitrogen intake continues), a positive balance obtains until a new lower metabolic level is reached, i.e., more nitrogen is deposited. These effects are much more marked in a person afflicted with myxedema than in a normal person. Indeed, as Boothby has suggested, the "edema" of myxedema may be an abnormal amount of deposit protein in and beneath the skin. The efficacy of thyroid therapy, previously noted, in reducing the increased proteins of the plasma and the albumin of the tissues, in cases of myxedema, supports the view that the thyroid gland is somehow associated with protein regulation and metabolism.

Although the foregoing review has brought out the primary importance of homeostasis of the proteins of the plasma for maintaining the volume and character of both the intravascular and extravascular fluid matrix of the organism, and for protecting the organism against loss of the essential part of the matrix—the blood—, it has revealed also how much still needs to be learned. Here, as with other useful material, constancy is attained by storage, which stands between plenty and need, and in this respect the liver plays an important rôle. The sympathico-adrenal apparatus seems to influence release from storage, and also varying activity of the thyroid gland may be determinative. Are special agencies required to manage the laying by of the reserves? We do not know.

Fat. According to Bloor (1922) the concentration of fat, cholesterol and lecithin in the blood is fairly constant in the same species of animals, but may differ greatly in different species. As is well known, ingestion of fat produces an "alimentary lipemia" which may cause the fat content of the blood to rise as high as 3 per cent in the dog and 2 per cent in man. A relatively large increase in the fat content of the blood appears to be without serious consequence. In pathological states —e.g., in diabetes—the lipemic percentage may rise to 10, 15 and even to 20 per cent without producing obvious symptoms. On the other hand the normal blood fat is remarkably persistent. Carbohydrate and protein alone may be fed for considerable periods without reduction of the lipemic level, and fasting for short periods may actually be accompanied by a rise (Schulz, 1896), although after two weeks of fasting the level may undergo a slow fall. Whether total absence of fat from the blood could be produced, and if so, whether that condition would be attended by disturbances, are questions yet to be answered.

The constancy of the lipemic level for many days in spite of relative or complete starvation implies that there is a governing agency which brings the fat from storage into the blood stream. As Lusk (1928, p. 107) has remarked, "The length of life under the condition of starvation generally depends upon the quantity of fat present in the organism at the start." Fat is stored in the liver, if carbohydrate is not fed (Rosenfeld, 1903); it is also stored under the skin, beneath serous coats (e.g., around the kidneys), in the omentum, and between and in the muscle fibres. What leads to fat storage in some individuals to a greater extent than in others is unknown. In hypothyroidism there may be a generally diffused obesity, an obesity which rapidly disappears under thyroid therapy. A slight scratch in the surface of the brain stem between the infundibular process and a mammillary body produces adiposity (Bailey and Bremer, 1921), as does a tumor or other lesion of this region. Grafe (1927) cites instances of unilateral hypertrophy or atrophy of fatty tissues and suggests that the disposal of fat is under a sympathetic control managed from the hypothalamic region. It is pertinent to note that kittens allowed to live after unilateral sympathectomy until they have doubled their weight, have no demonstrable differences in the amount or distribution of the fat on the two sides of the body (Cannon, Newton, Bright, Menkin and Moore, 1929).

If the regulation of fat storage is obscure, the regulation of its release is even more so. When fat is needed for maintaining the energies of the body it is removed from adipose tissue until the fat cells are practically empty. Yet, even when death from starvation occurs, the fat content of other tissues may not be very different from normal (Terroine, 1914). What causes the fat to move from the adipose stores is not known. Lusk's remark, that "the fasting organs attract fat from the fat deposits of the body, and it is brought to them in the circulating blood," was probably not intended to be explanatory, and it is not. Possibly the reversible reaction mediated by lipase, as described by Kastle and Loevenhart (see Loevenhart, 1902), may be an important factor in maintaining homeostasis of the lipemic level—the enzyme favoring storage when the level is raised and favoring release when the level falls. But on these points more information is desirable.

Calcium. The special and diverse uses of calcium—for the growth of the skeleton and teeth, for the repair of broken bone, for the maintenance of proper conditions of irritability of nervous and muscular tissues, for the coagulation of blood, and for the production of serviceable milk—render it a highly important element in the bodily economy. Like

sugar and protein and fat, calcium may be in great demand on exceptional occasions. Under such circumstances, however, the amount in the blood must not be much reduced, for serious consequences ensue. As previously noted, there is normally a homeostasis of calcium in the blood at approximately 10 mgm. per cent. If the blood calcium is lowered to less than 7 mgm. per cent, as may be done by removal of the parathyroid glands (without change in the percentage of sodium and potassium), or by injection of sodium citrate, twitchings and tetanic convulsions occur, with a severity measured by the degree of deficit of available calcium; and these symptoms are quickly relieved by injecting a soluble calcium salt sufficient to restore the normal percentage (MacCallum and Voegtlin, 1909; MacCallum and Vogel, 1913; Trendelenburg and Goebel, 1921). On the other hand, if the blood calcium is raised above approximately 20 mgm. per cent, by injection of parathyroid extract, profound changes are produced in the blood—the viscosity is greatly increased, the osmotic pressure rises, the blood phosphates are doubled, and there are four times the normal amount of non-protein and urea nitrogen—conditions associated with vomiting, coma, and a failing circulation (Collip, 1926). Obviously homeostasis of blood calcium is of capital importance.

As in the homeostasis of other materials, that of calcium is made possible by storage, built up in times of abundance and utilized in time of need. The recent studies of Bauer, Aub and Albright (1929) have demonstrated that the trabeculae of the long bones are easily made to disappear by a persistent diet deficient in calcium and by growth, and that they are readily restored by feeding a calcium-rich diet. The trabeculae serve, therefore, as a storehouse of conveniently available calcium.

How the homeostasis of calcium is regulated has not been determined. The following evidence associates the parathyroid glands with the regulation: 1. Partial or complete removal of these glands results in a lowering of the calcium content of the blood, as mentioned above, and in a defective deposit of dentine in growing teeth and in a defective development of the callus about a bone fracture (Erdheim, 1911). 2. A diet poor in calcium induces parathyroid hyperplasia (Marine, 1913; Luce, 1923); pregnancy and lactation do likewise, without, however, reduction of the calcium percentage in the blood. 3. Diseases characterized by defects in calcification of bone—e.g., rickets and osteomalacia—are attended by hypertrophy of the parathyroid glands (see Strada, 1909; Weichselbaum, 1914). And 4, implantation of parathyroids in a parathyroidectomized

rat restores the power to deposit dentine having a normal calcium content (Erdheim, 1911). But *how* the parathyroids control calcium homeostasis—whether they act directly or are stimulated by nerves, whether they act alone and by increased or decreased activity effect storage or release, or whether they coöperate with other agencies perhaps antagonistic—all this still needs investigation.

The pharmacodynamic action of thyroxin seems to involve the thyroid as well as the parathyroid glands in calcium metabolism (Aub, Bauer, Heath and Ropes, 1929). Administration of thyroxin greatly increases the calcium losses in urine and feces whether persons are normal or myxedematous. There is evidence also that in hyperthyroidism the bones show osteoporosis and that calcium excretion is much augmented. Possibly the parathyroids serve for deposit and the thyroids for release of calcium—thyroxin raises the blood calcium in a low-calcium tetany. Such hints, however, must be regarded with suspicion until put to test, for, as shown in the experiments on the action of adrenin and insulin, mentioned above, powerful pharmacodynamic agents given in doses exceeding the physiological range can produce complicated and indirect effects.

The homeostatic functions of hunger and thirst. In the foregoing discussions storage has been emphasized as a regulatory mediation between supply and demand. Back of storage, however, and assuring provisions which can be stored, are powerful motivating agencies—appetites and hunger and thirst. Because of pleasurable previous experiences with food and drink appetites invite to renewal of these experiences; thereby material for the reserves is taken in. If the reserves are not thus provided for, hunger and thirst appear as imperious stimuli. Hunger is characterized by highly disagreeable pangs which result from strong contractions of the empty stomach—pangs which disappear when food is taken (Cannon and Washburn, 1912; Carlson, 1916). Thirst is an uncomfortable sensation of dryness and stickiness in the mouth, which can be explained as due to failure of the salivary glands (which need water to make saliva) to keep the mouth moist; when water is swallowed and absorbed they, as well as the rest of the body, are provided with it and since they can consequently moisten the mouth, the thirst disappears (Cannon, 1918). By these automatic mechanisms the necessary materials for storage of food and water are assured.

Overflow. Previously, in relation to the homeostasis of blood sugar, the use of overflow as a means of checking an upward variation of constituents of the blood has been mentioned. Not only excessive sugar,

but excessive water, excessive sodium and potassium and chloride ions are discharged by the kidneys. In accordance with the modern theory of urine formation (Cushny, 1926), these are all "threshold substances." They are resorbed by the kidney tubules only in such relations to one another as to preserve the normal status in the blood. All in excess of that is allowed to escape from the body.

It is interesting to note that these substances are primarily stored by flooding or inundation. When these reserve supplies are adequate, however, the ability of the overflow factor to maintain homeostasis is marvelous. The feat reported by Haldane and Priestley (1915) of drinking 5.5 liters of water in six hours—an amount exceeding by one-third the estimated volume of the blood—which was passed through the kidneys with such nicety that at no time was there appreciable reduction of the hemoglobin percentage, is a revelation not only of the efficacy of the kidney as a spillway but also of the provision in the body for maintaining a constancy of its fluid matrix.

The lungs as well as the kidneys serve for overflow. As is well known, a slight excess of carbonic acid in the arterial blood is followed by greatly increased pulmonary ventilation. Thus the extra carbon dioxide is so promptly and effectively eliminated that the alveolar air is kept nearly constant (Haldane, 1922). By this means provision is made for extra carbon dioxide to flow out from the blood over a dam set at a fixed level. In consequence, in usual circumstances, the hydrogen-ion concentration of the blood is fairly evenly maintained, and the harmful effects of an excessive shift in the alkaline or acid direction is avoided.

HOMEOSTASIS BY REGULATING PROCESSES. There are steady states in the body which do, indeed, involve the utilization of materials, but which are so much more notably dependent on altering the rate of a continuous process that they can reasonably be placed in a separate category. We shall consider two of them, the maintenance of neutrality, and the maintenance of a uniform temperature (in homeothermic animals). The physiological adjustments involved in these processes are so commonly known that a mere outline of them, without detailed description or many references, will be sufficient to illustrate the mode of regulation.

Maintenance of neutrality. The importance of confining the changes in the hydrogen-ion concentration of the blood to a narrow range has already been emphasized. This concentration is determined by the ratio, H_2CO_3:$NaHCO_3$, in the blood. On going to a high altitude the tension of carbonic acid is lessened, the ratio is lowered and the pH rises.

Under these circumstances the blood alkali also is lessened until the pH is restored. And on returning to sea level the opposite process occurs and continues until there is a normal adjustment again, due, according to Y. Henderson (1925), to "calling an increased amount of alkali into the blood," a result probably attained, however, by the passage of acid elements from the blood into the tissues or the urine.

Back of these adjustments between the blood and the tissues, however, are the preventive measures which protect the blood from danger by anticipatory action. Acid metabolites are continuously being produced in the living cells and if allowed to accumulate in them these substances interfere with or prevent further action. Elaborate arrangements are ready in the organism to forestall that contingency. To be sure, the facilities for controlling non-volatile acid are limited. But it can be dealt with in a variety of ways. The lactic acid, for example, which is developed in muscular contraction, is in part promptly neutralized—the phosphocreatine recently discovered by Fiske and Subbarow (1929) appears to be capable of functioning in an extraordinarily effective manner in neutralizing lactic acid within the muscle cells. Another part of the acid is soon oxidized; and the rest is rebuilt into neutral glycogen. For continued effectiveness of all three of these methods of disposal there must be provided an adequate supply of oxygen. Although muscles, and probably other tissues as well, go into "oxygen debt" by acting in spite of accumulating lactic acid, that state is characterized by a diminished capacity to do work, great according to the debt, by a prescription on the amount of debt allowable, and by the definite requirement of ultimate payment. When non-volatile acid is burned to volatile carbonic acid, however, it is in a form which can be carried away and disposed of to an almost unlimited amount, with only slight change in the reaction of the blood. During vigorous muscular work as much oxygen as possible must be delivered. There is practically no storage of oxygen in the body. Air-breathing animals are surrounded by an ocean of oxygen—the problem is solely that of conveyance from the boundless external supply to the exigent tissues. For that purpose circulatory and respiratory processes must be greatly accelerated. Fortunately these adjustments, required to get rid of the volatile acid, are precisely those required to bring to the tissues the oxygen which serves to make the acid volatile and readily discharged.

In vigorous muscular effort the pulmonary ventilation may be increased from 6 liters per minute to 60 or 80 liters or more, due to the effects of acid in the respiratory center. Under these circumstances the

sympathico-adrenal system is active (Cannon and Britton, 1927) and it is altogether probable that thereby the bronchioles are dilated at a time when wider passageways would facilitate the to-and-fro movement of larger volumes of air. There is an ampler return of blood to the heart per minute, because of contraction of the splanchnic vessels, because of the pressures excited by the active muscles on capillaries and veins within them, and because of the pumping action of the diaphragm. Thus the heart receives a greater charge of blood and puts forth a greater amount per beat. And because of lessened vagal tone, increased tension on the venous side, and participation of the sympathetic accelerators, the heart, well charged, may beat twice as fast as it does at rest. With a much larger minute output from the heart and a constricted splanchnic area the arterial pressure is markedly raised. In the active muscles the arterioles are dilated and the closed capillaries are opened; and through these more numerous channels the high head of arterial pressure drives an abundant blood stream. Evidence indicates that the total circulation rate may be augmented as much as four times. But not only are the corpuscles utilized more effectively by being made to move faster, the *number* of corpuscles is increased by discharge from storage in the spleen (see Barcroft, 1926)—an effect which, like splanchnic constriction and cardiac acceleration, the sympathetic system helps to produce (see Izquierdo and Cannon, 1928). In the laboring muscles, where acid is being produced and where especially oxygen is needed, the excess carbon dioxide itself facilitates the unloading of oxygen from the corpuscles and also its own carriage away to the lungs. In these ways the local flow may be increased as much as 9 times and the oxygen delivery may be increased as much as 18 times what it is during rest (Bainbridge, 1923). Thus, in spite of the fact that in a short time more lactic acid by far can be produced by muscular work than could be neutralized by the buffers in the blood—a condition which must inevitably cause death—the reaction of the blood is altered to only a minor degree.

No more admirable example of homeostasis can be mentioned than that of the pH of the fluid matrix of the body. It is managed by accelerating and retarding the continuous processes of pulmonary ventilation and the flow of blood. The physico-chemical changes within the blood itself, which will not be considered in this article, greatly diminish the effects of slight variations in these physiological processes. The degree of respiration is largely influenced by the hydrogen-ion concentration in the cells of the respiratory center, but they in turn are

influenced by an increase of the concentration of carbonic acid in the blood. Again the disturbance brings its own cure, and as the concentration is lowered by the heavier breathing, the heavier breathing ceases. The adjustment of the circulation may be similarly managed. The faster heart, the vascular constriction (except in active areas), and the contracted spleen point to functioning of the sympathetic system. Even slight voluntary activity calls the system into service (Cannon and Britton, 1927), and asphyxia is a highly effective stimulus for it (Cannon and Carrasco-Formiguera, 1922). The centers for sympathetic control may be influenced like the respiratory center—acidity may develop in them as a consequence of oxygen-want or carbonic acid excess and the primary result may be stimulation. This suggestion is supported by the experiments of Mathison (1911), showing that asphyxia and also extra carbon dioxide in the respired air raise arterial blood pressure, and by the observation of Cannon, Linton and Linton (1924) that muscle metabolites bring into action the sympathico-adrenal system. In vigorous muscular work the remarkably close correlation between the adjustment of the respiratory and the circulatory apparatus to the needs of the organism might thus be explained,—though both systems are started into faster service by impulses incidental to a voluntary act, they might be maintained in the performance of their extra task by the increased hydrogen-ion concentration in the blood and later they would gradually return to their quiet routine functions because their extra activity had resulted in reducing the hydrogen-ion concentration to the resting level.

Maintenance of uniform temperature. The importance of uniform temperature in providing conditions favorable for a constant rate of the chemical changes in the body requires no emphasis. And the danger of a rise of temperature a relatively few degrees above the normal, as well as the depressant effect of a fall much below the normal, likewise is well recognized. For general considerations, to be discussed presently, it is pertinent, however, to mention briefly the changes which take place when the body temperature tends to rise or fall. If the change is in the direction of a rise, relaxation of peripheral vessels occurs, thus exposing warm blood to the surface where heat may escape to colder surroundings; or when that is ineffective, sweating takes place, the skin is cooled by evaporation, and the abundant blood flowing through the skin loses heat thereby. Polypnea plays a part similar to sweating, and is especially serviceable in animals not well provided with sweat glands. If, on the other hand, the change is in the direction of a fall, there is a constriction of peripheral vessels and an erection of hairs and feathers

which enmesh near the skin a layer of poorly conducting air; when these means of conserving heat do not check the fall of temperature, adrenin, capable of increasing heat production, is set free in the blood stream (Cannon, Querido, Britton and Bright, 1927); and when the heat thus produced does not suffice, shivering is resorted to as the final automatic protection against a temperature drop. This highly efficient arrangement for maintaining homeostasis of body temperature involves only an acceleration or retardation of the processes of heat production and heat loss which are constantly going on. The delicate thermostat which operates the regulation appears to be located in the subthalamus (Isenschmid, 1926; Rogers, 1920), and to be influenced directly by changes in the temperature of the blood (Kahn, 1904; O'Connor, 1919; Sherrington, 1924), and also reflexly (see Hill, 1921). The noteworthy features of the total arrangement, apart from its efficiency, are the varieties of the devices for homeostasis, their appearance in a sequence of defences against change, and the close involvement of the sympathetic system in the conservation, production and dissipation of heat.

THE RÔLE OF THE AUTONOMIC NERVOUS SYSTEM IN HOMEOSTASIS. The homeostatic regulators act automatically. Although skeletal muscles and the diaphragm are, of course, under control of the cerebral cortex, their functions in the regulation of temperature (shivering) and neutrality (faster breathing) are managed low in the brain stem. And for the most part the regulators are not under voluntary government. Commonly the autonomic system, or that system in coöperation with endocrine organs, is called into action. Illustrations of these facts are seen in the vago-insular and the sympathico-adrenal influences on the glycemic level, the vagal and sympathetic effects on the heart rate and the sympathetic effects on blood vessels during vigorous muscular effort, and the sympathico-adrenal function in accelerating heat production when the body temperature tends to fall.

The facts just mentioned emphasize a distinction long recognized between the "voluntary" and the "involuntary" or "vegetative" functions of the nervous system. It is desirable to remove from physiology terms having psychological and botanical implications. The two relations of the nervous system—towards the external and towards the internal environment—naturally suggest that distinctions should be based on these opposite functions. The "voluntary" or cerebrospinal system, elaborately outfitted with exteroceptors and with muscles which operate bony levers, is arranged for altering the external environment or the position of the organism in that environment by laboring,

running or fighting. These may appropriately be regarded as *exterofective* activities, and the "voluntary" system therefore as the exterofective system. The exterofective activities, however, must produce coincident changes in the internal environment—e.g., utilizing blood sugar and discharging into the blood acid waste and extra heat. Under these circumstances the "involuntary" nervous system plays its part by acting on the heart, smooth muscles and glands in such ways as will preserve the "fitness" of the internal environment for continued exterofective action. This interofective function of the "involuntary" nervous system justifies calling it the *interofective* system. Inactivity of the exterofective system establishes a basal state for the organism, because minimal functioning of that system is accompanied by minimal functioning also of the interofective system. Exterofective action is reflected in interofective action, which rises as the internal disturbance rises and subsides as the disturbance subsides.

The interofective system has been referred to thus far as if it were single instead of consisting of three divisions, with distinctive general functions. These functions were summarized by Cannon (1914) as follows—the sacral, a group of reflexes for emptying hollow organs which become filled; the cranial, a series of reflexes protective and conservative and upbuilding in their function; and the mid- or sympathetic division, a mobilizer of bodily forces for struggle. Similar views have been expressed by Hess (1926) who has recognized the "histotropic" function of the cranial division in promoting the welfare of the tissues, and the "ergotropic" function of the sympathetic division in operating to increase the facilities for doing work. The ideas developed in the foregoing discussion modify only slightly the views expressed in 1914. The emphasis is somewhat differently placed, to be sure, if the maintenance of conditions favorable for exterofective activity is regarded as the chief function of the autonomic system. Thus, although the sacral autonomic division has as one of its functions the perpetuation of the race, it is also serviceable in emptying the bladder and rectum of loads which might interfere with extreme physical effort—an interpretation which is consistent with the well-known effects of strong emotion (e.g., fear) in voiding these viscera as a preparation for struggle. Likewise, though the cranial division has other conservative functions it notably exhibits its conservative uses in providing and preserving the measures which are required to keep the fluid matrix constant when profound disturbance might occur: it gives the heart opportunity for rest and recuperation by checking its rate in quiet times, it promotes the gastro-intestinal move-

ments and excites secretion of the digestive juices and thereby assures the reserves of energy-yielding material, and it appears to be further useful through the vago-insular system in bringing into storage some of these reserves. These divisions, the sacral and the cranial, however, operate indirectly and somewhat remotely to protect homeostasis. It is the mid- or sympathetic division which acts directly and promptly to prevent changes in the internal environment; by mobilizing reserves and by altering the rate of continuous processes; as repeatedly noted in the foregoing pages, this division works to keep constant the fluid matrix of the body and therefore may properly be regarded as the special and immediate agent of homeostasis. The idea that the sympathetic division—or the sympathico-adrenal apparatus, for the nerve impulses and adrenin coöperate—serves to assure homeostasis, that for this purpose it functions reciprocally when the exteroceptive system functions, is not a fundamental modification of the "emergency theory" (Cannon, 1914a). Recent studies have shown that if emergencies do not arise, if marked changes in the outer world or vigorous reactions to it do not occur, the sympathico-adrenal apparatus is not a necessity and can be wholly removed without consequent disorder (Cannon, Newton, Bright, Menkin and Moore, 1929). Limitations appear when circumstances alter the internal environment; it is then that the importance of the sympathico-adrenal apparatus becomes evident. As has been shown above, however, this apparatus plays its rôle not only in preserving homeostasis during grave crises which demand supreme effort, but also in the minor exterofective adjustments which might change the fluid matrix of the body.

SOME POSTULATES REGARDING HOMEOSTATIC REGULATION. About four years ago Cannon (1925) advanced six tentative propositions concerned with physiological factors which maintain steady states in the body. It will be pertinent to consider them again now with reference to the foregoing discussion of homeostasis.

1. "In an open system such as our bodies represent, compounded of unstable material and subjected continually to disturbing conditions, constancy is in itself evidence that agencies are acting, or ready to act, to maintain this constancy." This is a confident inference—an inference based on some insight into the ways by which certain steady states (e.g., glycemia, body temperature, and neutrality of the blood) are regulated and a confidence that other steady states are similarly regulated. The instances cited in the previous pages have illustrated various agencies employed in the organism to that end. Although we do

not know how constancy of plasma proteins, lipemia and blood calcium, for example, is brought about, probably it results from as nice devices as those operating in the better known cases of homeostasis. Of course this realm of interest is full of problems—highly significant problems—inviting attempts at solution, and as they are solved the confidence expressed in the first postulate may be justified.

2. "If a state remains steady it does so because any tendency towards change is automatically met by increased effectiveness of the factor or factors which resist the change." Thirst, the hypoglycemic reaction, the respiratory and circulatory response to a blood shift towards acidity, the thermogenic functions, all become more intense as the disturbance of homeostasis is more pronounced, and they all subside promptly when the disturbance is relieved. Similar conditions probably prevail in other steady states. Of course, the state may not remain steady, as in pathological weakness or defect, and for that reason the postulate was made conditional. As Lotka (1925) has pointed out, this conditional statement, required for living beings and due to their lack of permanent stability, sharply distinguishes the proposal from the strict principle of Le Chatelier true for simple physical or chemical systems. Indeed, as Y. Henderson (1925) has remarked, the physiological and the chemical conceptions of equilibrium are quite different. "The one invokes energy to maintain itself, or if disturbed to recover . . . . . the other in seeking balance only goes down hill dynamically."

3. "Any factor which operates to maintain a steady state by action in one direction does not also act at the same point in the opposite direction." This proposal, which should have been limited to *physiological* action, is related to the questions discussed in the footnote on p. 410. Does adrenin in physiological doses both discharge glycogen from the liver and increase glycogen storage there? Does insulin likewise act oppositely in relation to the hepatic glycogen reserves? In the footnote mentioned, reasons were given for not crediting the evidence for opposed action by a single one of these agents. An agent may exist which has an influence of a tonic type—a moderate activity—which can be varied up or down, and which can act at a given point in "high" concentration but not in a "low" concentration. The adrenal medulla, which is subject to control of opposed nervous influences (Cannon and Rapport, 1921), may be cited as an agent of that type.

4. "Homeostatic agents, antagonistic in one region of the body, may be coöperative in another region." The sympathico-adrenal and the vago-insular influences are opposed in action on the liver, but they

appear to be collaborators in their action on muscles, e.g., leading to effective use of sugar by muscle cells (Burn and Dale, 1924). Too little is known about the effects of these agents to permit this postulate to be of much significance at present.

5. "The regulating system which determines a homeostatic state may comprise a number of coöperating factors brought into action at the same time or successively." This statement is well illustrated in the arrangements for protection against a fall of temperature in which series of defences are used one after another, and also in the elaborate and complex arrangements for maintaining uniform reaction of the blood.

6. "When a factor is known which can shift a homeostatic state in one direction it is reasonable to look for automatic control of that factor or for a factor or factors having an opposing effect." This postulate is implied in earlier postulates. It is expressed as a reiteration of the confidence that homeostasis is not accidental but is a result of organized government, and that search for the governing agencies will result in their discovery.

The reader has had occasion to be impressed by the large gaps in our knowledge not only of homeostatic conditions but also of the arrangements which establish and maintain them. Repeatedly the phrase "is not known" has had to be employed. It is remarkable that features so characteristic of living beings as the steady states should have received so little attention. Innumerable questions remain to be answered. Little is known, for example, about the effective stimuli for such homeostatic reactions as are well recognized. Are there receptors which are affected in blood-sugar regulation or are the regulatory factors worked by direct action on cerebral centers? Again, there are homeostatic agencies which were not considered above, such as the extra erythrocytes produced in organisms living at high altitudes, the thicker hair growth during prolonged cold weather, and also steady states which have not been mentioned, such as the stabilization of phosphorus in relation to calcium, the evidence from constancy of basal metabolism that there is constancy in the thyroxin content of the blood, indeed the evidence from other steady states (as weight, and sex character) that other endocrine products are uniformly circulating—the questions presented by these and many other reactions which are serviceable in preserving uniformity in the fluid matrix offer a fascinating field for research.

In the two preceding sections the functions of the divisions of the autonomic system in relation to homeostasis were defined and some

postulates regarding homeostasis were presented, not with the idea that the statements should be taken as conclusive but rather that they might prove suggestive for further investigation. Indeed, that point of view should be recognized as prevailing throughout this review. It is the writer's belief that the study of the particular activities of the various organs of the body has progressed to a degree which will permit to a greater extent than is generally recognized an examination of the interplay of these organs in the organism as a whole. Their relations to their internal environment seemed to offer a suggestive approach to a survey of their possible integrative functions. In such a venture errors are sure to creep in which must later be corrected, and crude ideas are sure to be projected which must later be refined. Though the present account of agencies which regulate steady states in the body is likely to prove inadequate and provisional, there is no question of the great importance of the facts of homeostasis with which it deals. This account may at least serve to rouse interest in them and their importance. The facts are significant as outstanding features of biological organization and activity. They are significant also in understanding the complex disorders of the body, for in a state normally kept regular by a group of coöperating parts, full insight into irregularity is obtained only by learning their mode of coöperation. Again, effective methods of attaining homeostasis are significant in comparison with the methods in systems where steady states are not yet well developed; the regulation of homeostasis in higher animals is probably the result of innumerable evolutionary trials, and knowledge of the stability which has finally been achieved is suggestive in relation to the less efficient arrangements operating in lower animals and also in relation to attempts at securing stability in social and economic organizations. Finally, continued analysis of biological processes in physical and chemical terms must await a full understanding of the ways in which these processes are roused to perform their service and are then returned to inactivity. Indeed, regulation in the organism is the central problem of physiology. For all these reasons further research into the operation of agencies for maintaining biological homeostasis is desirable.

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THE POSITION OF PHOSPHORUS IN THE CHEMICAL MECHANISM OF MUSCULAR CONTRACTION

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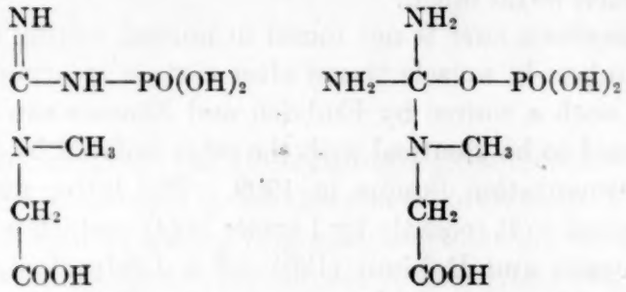
We have been accustomed for several years to think of the significance of phosphorus in muscles in terms of the measured quantities "inorganic phosphate" and "lactacidogen," which between them accounted for the greater part of the acid-soluble phosphorus of a muscle (the acid-insoluble part is small, consists mainly of lipoid, and appears to be of structural value only). It has been found in the last two years that most of this "inorganic" phosphate is really organic, and most of the "lactacidogen" is inorganic (pyro) phosphate. These two discoveries, which it may be noted, were in themselves of a purely chemical nature, threw doubt on the validity of almost all earlier physiological studies of the phosphorus changes in muscle, and the more important experiments have had to be repeated with new chemical techniques. The re-assessment of the value of earlier results is still going on in the laboratories of Embden, and Meyerhof, and elsewhere, and the process is not yet complete. This being so, no apology seems necessary for the purely chemical nature of the first part of this review.

The study of the phosphorus compounds isolated by chemical treatment from muscle has led to the identification of four or five which probably play a part in the chemical processes concerned in contraction and relaxation. The chemical properties of these compounds are discussed without reference, for the moment, to their real or supposed physiological functions.

Orthophosphoric acid was isolated in the form of its acid potassium salt from muscles by Valenciennes and Fremy (116), 74 years ago. The amount present in resting muscles is very small indeed—representing less than one-tenth of the total phosphorus—and in the faintly alkaline condition of the resting muscle it is about three-fifths neutralised. It is an efficient buffer in the range pH 7.4 to 6.0, which is approximately the range over which an isolated muscle varies in passing from rest to extreme fatigue.

Pyrophosphoric acid has the constitution represented by $PO(OH)_2-O-PO(OH)_2$, but it does not appear to form more than two series of salts. Its titration curve contains four breaks, corresponding to four titration constants, the values of which are given in table 1. Its presence in muscles (to an extent accounting for 15 per cent of the total phosphorus) has only recently been discovered—by Lohmann, who isolated it in the form of two derivatives: the diaquotetramminecobaltipyrophosphate $(Co(NH_3)_4(OH_2)_2\ 4(P_2O_7)_3)$, and the sodium salt. The alkali pyrophosphates are formed when the corresponding orthophosphates are heated to red heat; they are rapidly hydrolysed by boiling in acid solutions. The hydrolysis takes a few minutes only in normal hydrochloric acid. Pyrophosphate does not diffuse out of living muscles (76).

Creatinephosphoric acid was isolated by Fiske and Subbarow, and by Eggleton and Eggleton, from mammalian skeletal muscle in 1927 (6) (47). In resting frog muscles it accounts for two-fifths of the total phosphorus. The structure assigned to it by Fiske and Subbarow and by Lohmann (27) is given by formula I, but the alternative II is possible.



I II

The latter involves the presence of one molecule more of water in the formula. The barium and calcium salts both contain "water of crystallisation" which can only be removed with difficulty (several hours at 100° over P_2O_5 in vacuo). The anhydrous material finally obtained gives analysis figures which favour formula I, but it is possible to suppose that the change brought about by the desiccation treatment is more profound than the removal of "water of crystallisation." Neither formula is given here with any confidence: rather is it sought to emphasize the uncertainty of both. More work is necessary before the structure may be regarded as settled, and it must not be overlooked that the structure of creatine itself is not known with certainty. Creatinephosphoric acid has very soluble barium and calcium salts; it is apparently optically inactive and has apparently no copper-reducing power,

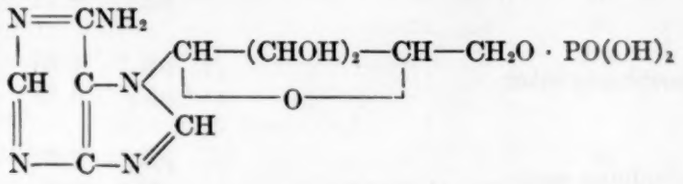
but no exact studies of these properties on pure preparations have yet been published. Its most remarkable characteristic is its rapid hydrolysis by even weak acids to creatine and orthophosphoric acid. It is half hydrolysed by N/4 trichloracetic acid in 200 minutes at 18° (105) and by N/1 HCl at 20° in 130 minutes (27). The hydrolysis is catalysed by the presence of molybdic acid. About 11,000 calories are evolved per gram-molecule of the compound hydrolysed (121). As would be expected from its low molecular weight it dialyses rapidly through collodion. It does not appear to dialyse from living muscle (48) and may therefore not be present in the living muscle in a free condition. For this and other reasons it has been thought best to retain the term "phosphagen" for the substance present in the muscle, reserving the chemical name creatinephosphoric acid for the compound present in protein-free extracts. Unlike creatine, arginine and certain other substituted guanidines (122), it does not react with diacetyl, or with phenyl methyl diketone, in alkaline solution to give a coloured product (105). In this respect it resembles creatinine. All attempts to synthesise this acid have so far failed.

Hexosediphosphoric ester is not found in normal resting muscles, but it may accumulate in muscle tissue after certain treatments. It was isolated from such a source by Embden and Zimmerman (1) in 1924, and it was found to be identical with the ester isolated by Young (115) from yeast fermentation liquors in 1909. The latter may have the structure assigned to it recently by Levene (123)—which was suggested earlier by Morgan and Robison (129)—of a 1-6-fructosediphosphoric ester, but the evidence available so far is not sufficient to enable us to decide with certainty on the details of its structure. The titration constants of the phosphoric acid groups are given in table 1; like most substituted orthophosphoric acids it is a stronger acid than orthophosphoric. The free ester is slightly dextro-rotatory ($[\alpha]_D^{20}$ 3.5°), and becomes laevo-rotatory on hydrolysis. One of the phosphoric acid groups is easily removed, the second is more resistant.

Hexosemonophosphoric ester was recently discovered in muscle by Embden and Zimmerman (4), who found it to differ in certain respects from the ester which Robison (3) had isolated in 1922 from yeast fermentations. This difference may be less than was at first thought, for both esters seem to be mixtures in varying proportions of an aldonic and a ketonic ester. Embden's preparation from muscle appeared to be almost exclusively aldonic, with a specific rotation of +29.5° (D line). Lohmann has found (27) evidence indicating that the ketonic component

in Robison's ester is more rapidly hydrolysed by acid than the aldonic fraction. Pryde (2) has recently isolated Embden's hexosemonophosphoric ester from muscles of goats, donkeys, and rabbits, and found on oxidation and dephosphorylation a large yield of gluconic acid. He concludes that the ester is mainly glucosemonophosphoric ester. See also Neuberg and Liebowitz (61). The phosphate radicle of Robison's ester is thought by Morgan and Robison (62) to be on the fifth carbon atom; an opinion formed independently by Levene and Raymond (64).

Adenylic acid (adenosinephosphoric acid) has the structure represented by I: *Inosinic acid* is the deaminated derivative of adenylic acid. They are derived from the purines adenine and hypoxanthine by conjugation with d-ribose and phosphoric acid. Their titration constants are included in table 1. Over the range pH 5.0 to 8.0 their titration curves differ very little.



I

The relative amounts of all these substances, and certain others which will have to be considered in the discussion, present in the protein-free filtrate from a typical resting frog gastrocnemius are set out in table 2 below. Most of the figures are subject to large variation and the table must only be used as a rough guide.

METHODS, CHEMICAL AND PHYSIOLOGICAL. The analytical methods used in the 19th century for the estimation of orthophosphate in physiological fluids rested on the precipitation of phosphorus by uranium, by ammonium molybdate and by magnesia mixtures. They were as a rule gravimetric, and necessitated working on a rather large scale. The results obtained in the case of muscle analyses were vitiated by this fact since it was impossible to kill instantaneously a large mass of tissue, and the use of cooling devices had not been introduced. In 1914 Taylor and Miller (11) introduced a modification of the ammonium molybdate method in which the ammonium phosphomolybdate precipitate was filtered off and estimated colorimetrically by reduction of the molybdenum to a derivative which has an intense blue color. In this form the method does not appear to have been used for the study of muscles, but it formed the basis of most of the methods which have since

become popular. Bell and Doisy (12) found that hydroquinone was capable, in certain circumstances, of reducing ammonium phospho-

TABLE 1

SUBSTANCE	DISSOCIATION CONSTANTS*	REFERENCES
Orthophosphoric acid	pK_1' 1.98 pK_2' 6.82 pK_3' 11.9	96, 97, 117, 119
Pyrophosphoric acid	pK_1' 0.85 pK_2' 1.96 pK_3' 6.54 pK_4' 8.44	89
Hexosemonophosphoric ester	pK_1' 0.96 pK_2' 6.11	87, 96
Hexosediphosphoric ester	pK_1' 1.48 pK_2' 6.29	126, 96
Creatinephosphoric acid	pK_1' 2.7 pK_2' 4.6	121
Adenylic acid	pK_1' 3.8 pK_2' 6.2	90
Inosinic acid	pK_1' 2.4 pK_2' 6.4	90
Argininephosphoric acid	pK_1' 2.8 pK_2' 4.5 pK_3' 9.6	121
Arginine	pK_1' 4.97 pK_2' 11.90 pK_3' 12.84	124
Creatine	pK' 2.62	60

* No attempt is made here to relate the constants to specific groups in the molecule since in several cases this is still the subject of dispute (see Brönsted, 130).

molybdate without reducing any ammonium molybdate which might be present in the solution. This removed the necessity for filtration, and made the method applicable to very small quantities of tissue. The

reduction was carried out in alkaline solution in which the blue colour is unfortunately not stable. Briggs (13) found that the blue colour though less intense was far more stable if formed in acid solution, and his method, improved in various details (14, 23, 24) has been adapted for use in fermentation work (15) and muscle studies (16) (17). Only one other method has been widely used for muscle analyses: that published by Embden (18) in 1921, in which the orthophosphate is precipitated as strychnine phosphomolybdate and estimated gravimetrically. A colorimetric modification of it was suggested by Terada (19).

TABLE 2

SUBSTANCE	PARTS PER 100,000 OF MUSCLE	REFERENCE
Glycogen	700	
Lactic acid	20	
"Free creatine"	95	28, 29*
"Combined creatine"	275	29
Ammonia	1.5	91
Phosphoric acid derivatives (in terms of P):		
Orthophosphoric acid	15	20, 106
Creatinephosphoric acid	65	105
Hexosemonophosphoric ester	8	110
Hexosediphosphoric ester	trace ?	2, 4
Pyrophosphoric acid	25	76
Adenylic and Inosinic acids	20	93
Other acid-soluble phosphorus	10–20	

* Estimated by Walpole method.

The "total acid-soluble phosphorus" (the phosphorus present in a trichloracetic extract of a muscle) is estimated by any of the above methods preceded by a wet ashing process. The total phosphorus of the muscle is estimated in the same way. These three determinations gave (by difference) what was called the "inorganic," the "acid-soluble organic" and the "residual" phosphorus of the muscle. They are interpretable into recent terminology as follows:

"Inorganic" phosphorus = orthophosphate + phosphagen
"Acid-soluble organic" phosphorus = pyrophosphate + acid-soluble organic phosphates other than phosphagen.

The terms "total acid-soluble phosphorus" and "residual phosphorus" remain unaffected.

The methods now used are the above ones, coupled with separate determinations of the orthophosphate *or* phosphagen, and the separate determination of pyrophosphate. The pyrophosphate is estimated by Lohmann (89) by determining the increase in directly estimatable phosphorus (i.e., ortho- and creatinephosphoric acids) in a trichloracetic acid extract, resulting from a 7-minute boiling with normal hydrochloric acid. Any creatinephosphoric acid originally present is included in the first estimation, and the orthophosphate to which it gives rise during the boiling is included in the second. It therefore does not affect the difference.

To estimate the true orthophosphate of muscle Eggleton and Eggleton (21) tried precipitation in alkaline solution with magnesia mixture, and also a slightly modified form of the method of Bell and Doisy. But the most promising results were obtained by a modification of Briggs' method in which the rate of colour development in a test solution prepared from the muscle was compared with that of an inorganic orthophosphate standard. Fiske and Subbarow (47) adopted a similar device, using however their own modification (16) of Briggs' method. Lohmann (27) has obtained satisfactory results by precipitating the inorganic orthophosphate in alkaline solution with magnesia citrate, followed by a colorimetric estimation by his and Jendrassik's modification (17) of Briggs' method. Recently Sacks and Davenport (106), apparently unaware of Lohmann's work, have adopted the same principle, using a magnesia mixture. The methods of Fiske and Subbarow and of Eggleton and Eggleton have the advantage that they serve for the simultaneous estimation of creatinephosphoric acid.

Embden and Jost (110) have recently published a method for the estimation of hexosemonophosphoric ester in muscles, which consists in the precipitation as magnesium salts of most of the other phosphates from a protein-free filtrate of the muscle, followed by the precipitation of the ester by the further addition of ammoniacal alcohol. The reducing power of this precipitate toward the Hagedorn Jensen reagent is said to be proportional to the amount of hexosemonophosphoric ester present. Lohmann (76) has attempted to use the same principle but reports that it cannot be used in cases where hexosediphosphoric ester is present.

No satisfactory method is known for the direct estimation of creatine in the presence of creatinine and creatinephosphoric acid, but the problem will be rarely encountered, for blood and urine apparently contain no phosphagen, whilst muscles contain no creatinine. The

direct estimation of creatine in urine was achieved by Walpole (28) with a method based on the production of a pink colour when creatinine reacts with diacetyl in alkaline solution. Eggleton and Eggleton (105) observed that creatinephosphoric acid, like creatinine, failed to give this colour reaction, and were able to obtain a rough estimate of the non-phosphagen creatine in skeletal muscles. The method has been adapted by Dulière (29) for muscle analyses but its accuracy is still not very high. More promising results have been recently obtained (30) by precipitating the creatinephosphoric acid as the barium salt in slightly alkaline 60 per cent alcohol, leaving the non-phosphagen creatine to be estimated by the more satisfactory method of Folin.

In addition to the "inorganic" and "acid-soluble organic" phosphate of muscles, another phosphorus fraction has been measured and discussed in the literature of the last twelve years. This is the "organic" phosphorus which becomes "inorganic" when the minced muscle is incubated in a bicarbonate buffer at 40° to 44° for 2 hours. It was called by Embden (67) the "lactacidogen phosphorus," (and will be referred to in this paper as the "L" fraction). Its exact significance will be discussed in a later section.

The important effect of the method of killing a muscle upon the resulting analytical figures was not realised until the publication of the work of Fletcher and Hopkins (65) in 1907 on the lactic acid content of amphibian muscles. They showed for the first time the paramount importance of rapid grinding and demonstrated the advantage of using ice-cold killing agents. It is now known that true values for the lactate and inorganic orthophosphate contents of a muscle cannot be obtained unless the muscle is cooled thoroughly before grinding and ground rapidly in ice-cold reagents. Some workers indeed favour the use of liquid air for the quick killing of small muscles.[1] By slowly cooling isolated frog muscles at 0°C. in oxygen, and grinding them with sand in ice-cold trichloracetic acid, Eggleton and Horton (48) obtained values as low as 12 mgm. per cent for the inorganic orthophosphate content. Sacks and Davenport (106) by carefully cooling the muscles of warm-blooded animals in situ with a mixture of ethyl chloride and carbon dioxide snow obtained values ranging between 15 and 25 mgm. per cent.

Historical. That inorganic phosphate is liberated as a result of muscular activity has long been suspected. Engelmann (26) found

[1] This technique is very convenient, but somewhat risky if the muscle is not small (say, less than 200 mgm.) and thin. Even liquid air takes time to freeze the muscle, which is a very bad heat conductor.

increased urinary phosphate in a man after exercise. Weyl and Zeitler (31) in attempting to explain the increased acidity of excised muscles when fatigued stated that orthophosphoric acid was formed. Their chemical technique was however faulty. They were probably measuring something approximating to the total acid-soluble phosphorus. In 1895 Klug and Olsavsky (32) found the inorganic phosphorus excretion of a dog doubled by a day of hard exercise, and expressed the opinion that this inorganic phosphate was formed in the muscles. Macleod (33) in 1899 repeated the work of Weyl and Zeitler with an improved chemical technique, and reported a decrease in the amount of organic phosphates (or, as we should now say, acid-soluble phosphorus other than phosphagen and free orthophosphate) as a result of fatigue. The effect of exercise on the urinary excretion of phosphate was again noticed in 1903 by Garratt (34), but no such effect was observed by Mathison (35) in 1909.

In 1914 an attempt was made by Laquer (37), working in Embden's laboratory, to demonstrate a breakdown of organic phosphates with a production of orthophosphate as an accompaniment of fatigue in isolated frog muscles; in this he was unsuccessful, though confirming earlier workers in finding a loss of "organic" (which included pyro-) phosphate accompanying the onset of rigor.

Costatino failed to find any change in the "inorganic" phosphate content of rabbit muscles fatigued in situ (38), but Cohn (39) reported an increase. Embden in 1921 observe a rise in the phosphate excretion of men as a result of hard work (40), a result also reached by Campbell and Webster in 1922 (98). Embden and Lawaczeck (42) made a careful study of the "inorganic" phosphate changes in frog gastrocnemii fatigued in various ways; for reasons already discussed their method of analysis was incorrect but their results may be interpreted as showing that the sum of the inorganic (ortho-) and phosphagen phosphorus was slightly higher immediately after a short tetanus than it was a minute or two later. They affirmed their opinion that if muscular contraction was initiated by hydrogen ions those hydrogen ions came from phosphoric acid and not from lactic.

Cuthbertson (43) using anesthetised cats found that stimulation resulted in a large increase in the "inorganic" phosphate of the muscles (which probably means a liberation of orthophosphate from some compound other than phosphagen) and an extremely large rise in the orthophosphate concentration of the blood (which was doubled in 50 minutes' stimulation). He found no alteration in the amount of ether-soluble phosphorus in the muscles. Milroy (22) similarly noticed an

increase—as much as 50 per cent—in the "inorganic" phosphate of the gastrocnemii of cats, fatigued in situ by electrical stimulation. Directly opposed results with respect to muscle were obtained by Andrews (77). In 1926 Embden and Hentschel (45) studied the effect of severe fatigue on isolated frog muscles, and reported that the "inorganic" phosphate began to increase in amount after a long series of shocks. Havard and Reay (46) in the same year found that in short spells of vigorous exercise in man the orthophosphate level of the blood rose considerably.

The discovery in 1927 that most of the "inorganic" phosphate of a resting muscle was not inorganic (Eggleton and Eggleton, 20, 21), and in 1928 that a fair proportion of the "organic" phosphate was probably not organic (Lohmann, 89) has necessitated a complete reduplication of the earlier work. This reëxamination is at present very incomplete, and since no one worker has studied the simultaneous changes of the four or five compounds known, it is necessary to fit together results of different workers in order to obtain anything resembling a coherent picture. This is an unsafe proceeding, and leads in this instance to contradictory results—a clear indication that the physiological factors affecting the behaviour of a muscle are not yet standardised.

A muscle resting undisturbed in the body of a vertebrate probably contains little, if any, more orthophosphate per unit volume than the blood circulating through and around it. The most careful attempts to estimate the orthophosphate concentration in such muscles have led to figures ranging between 0.015 and 0.020 per cent of phosphorus, (rabbit, cat, dog, guinea pig (106), frog (56)), but such is the sensitiveness of the muscle to handling (as reflected in the appearance of orthophosphate) that one would not be surprised to find even lower values as the techniques of dissection and freezing are improved. Irving and Bastedo have shown that even restriction of the blood supply results in a rapid production of orthophosphate in the muscle (44). The phosphagen content of the muscle depends on its type and function. Plain muscle appears to contain none (105), heart muscle a small quantity (0.005–0.01 per cent P), "red" skeletal muscle considerably more, and "white" skeletal muscle would seem—on the basis of the very scanty evidence so far put foward—to be richest, containing usually about 0.060 per cent of phosphagen P. The amount of hexosemonophosphoric ester may vary in a similar manner, for Pryde (2) records considerably greater yields from "the more quickly-acting rabbits' muscle than from that of the larger and more slowly moving animals" (goat and donkey). The amount of pyrophosphate in frog gastrocnemii corresponds to about

0.025 per cent P: Lohmann (107) reports that in the frog (R. temp.) pyrophosphate is most abundant in the skeletal muscles. The tissues examined fall into the following order of decreasing pyrophosphate content: gastrocnemius, spleen, heart, nerve, testis, liver, stomach. All the tissues examined contained some, though blood cells contain only a tenth of the amount in muscles.

Studies of the behaviour of surviving excised muscles are necessarily restricted to the muscles of coldblooded animals. It is found that isolated frog muscles kept in oxygen do not show any changes suggestive of death; on the contrary, the amount of orthophosphate may decrease, particularly in the sartorius muscle, to values as low as 0.01 per cent P, with a corresponding increase in the amount of phosphagen. The coraco-mandibular muscle of the ray (R. clavata.) behaves in a similar way (Eggleton and Eggleton, unpublished). Pyrophosphate remains practically unchanged in oxygen (frogs) (76). The other phosphorus compounds have not been studied in this connection. There is however a tendency (strongly marked in sartorii) for the muscle to become inexcitable (Dulière and Horton, 63). This effect can be prevented or reversed by immersion of the muscle in (among other solutions) Ringer's fluid containing sufficient orthophosphate to prevent loss of the latter by diffusion (loc. cit.), and it would appear therefore to be an effect not directly connected with the phosphorus changes referred to.

Muscles kept in nitrogen or hydrogen steadily lose their phosphagen and become richer in orthophosphate. In the later stages other phosphoric esters break down, and also pyrophosphate (76), for when the muscle has reached the condition of rigor fully 70 per cent of its phosphorus is present as orthophosphate. Eggleton and Eggleton (105) found in the case of the coraco-mandibular muscle of the ray (R. clavata) that the increase in orthophosphate was exactly equalled by the loss of phosphagen, until only 5 to 15 per cent of the latter remained; only then was it possible to observe any unreversed breakdown of other phosphorus derivatives. It was incidentally observed that these changes were not connected in any simple manner with the production of lactic acid. These survival changes were, however, affected to an unknown extent by a slight degree of injury due to unavoidable cutting.

Fatigue of skeletal muscles in intact animals has been the subject of a few recent publications, and it seems that fatigue induced fairly rapidly results in the liberation of orthophosphate and the disappearance of phosphagen. Quantitative relationships have not been established, and indeed will be very difficult to work out, owing to the complications

introduced by the blood stream. For example, Irving (125) found the sum "orthophosphate plus phosphagen" sometimes to increase, sometimes decrease, slightly, in cat muscles fatigued in situ, with circulation intact. Large changes in the water content of the exercising muscle also obscure the issue (22) (see also Irving and Bastedo, 44). No direct evidence is yet available as to the changes occurring in hexosemonophosphoric ester, or pyrophosphate in these conditions. It is possible to infer from some recent work of Embden and his colleagues, referred to in a later section, that there may be a change of adenylic to inosinic acid, a change which does not involve any liberation of orthophosphate.

All these changes, if not artefacts, must necessarily be reversible, in the sense that the muscles must ultimately return to their original condition, but it is important to remember that this physiological reversibility does not imply the reversibility of any and every chemical reaction accompanying the muscular activity.

A tetanus of a few seconds' duration produces in the isolated gastrocnemius of the frog an easily measurable rise in the orthophosphate content, and a disappearance of phosphagen which may be more than sufficient to account for this rise. The phosphagen disappearance not accounted for by the orthophosphate production has been traced by Eggleton and Eggleton (105) to the formation of phosphorus compounds belonging to the "L" fraction, an observation recently confirmed by Sacks and Davenport (25), who were able to show further that only the acid-stable part of this fraction was increased. The remainder of this fraction (hydrolysed by 60 minutes' boiling in acid, and including Lohmann's pyrophosphate) was not found to alter in amount. Embden and Jost (110) have recently shown that a muscle (A) given 5 seconds' tetanus (and 30 seconds' rest) contains more hexosemonophosphate than a companion muscle (B) given only a single twitch (and killed whilst contracted). Since hexosemonophosphate is probably a constituent of the "L" fraction[2] this might be interpreted as a confirmation of the experience of the Eggletons, but Embden interprets the results in the opposite sense (as showing reformation of hexosemonophosphate during the recovery period). Embden's interpretation rests upon his observation that the recovering muscle (A) is not stimulated by contact with liquid air (shows "keine oder doch nur ganz geringfügige Kontractions-

[2] Embden and Jost (110) find that only part of the mono-ester is destroyed in the incubation technique which measures the "L" fraction.

erscheinungen"), and is therefore "fixed" in a relaxed condition, whilst B is killed in the active contracted state. Embden and Jost confirm Embden's earlier experience that resting muscles are stimulated by contact with liquid air (see Embden and Lawaczeck, 42).

It was early noticed that there was no fixed relationship between orthophosphate production and lactate production in the activity of isolated muscles (56), and Nachmansohn has emphasised this point in a detailed study of the phenomena. He reports (55, 59) that whilst the rate of lactate production during an isometric tetanus is proportional to the tension developed and is the same whether the muscle is curarised or not, the phosphagen breakdown is much less in the curarised than in the normal muscle. The ratio of phosphagen disappeared to lactate formed (expressed in mgm.-mols. of orthophosphate and mgm.-mols. of lactate respectively) has approximately the value 1.9 for 5 second tetani in the case of normal muscles directly stimulated, but in curarised muscles the value is only 0.8 to 1.0. Even in normal muscles the ratio diminishes as the muscle fatigues. There is here an indication that phosphagen has a function related to the phenomena of excitation, as distinct from contraction. Nachmansohn also records that during the few seconds following a short tetanus there is a reappearance of phosphagen, to the extent of 20 to 30 per cent of that which had disappeared during the tetanus, and this occurs in strictly anaerobic conditions. Gorodissky (57) has also observed this effect, and studied it in some detail, with essentially similar results. This "anaerobic restitution" ceases always before the phosphagen is all replaced. The aerobic restitution previously observed by the Eggletons continues further, until all the orthophosphate which had been liberated is removed again. It would seem that a certain part of the restitution process requires oxygen, perhaps because it is strongly endothermic. Yet even the "oxidative" restitution process is considerably more rapid than the oxidative removal of lactic acid (56).

Little is known of the behaviour of creatine during these various changes. The amount of free creatine in a resting frog gastrocnemius is roughly equivalent, molecule for molecule, to the amount of free orthophosphate (Duliere, 29); though sometimes more, it is never less. It is increased in amount as a result of fatigue (29) (56), but it is not possible yet to decide whether this increase accounts completely for the phosphagen disappeared.

Nachmansohn (loc. cit.) finds that the production of ammonia in fatigue is not directly connected with "phosphagen breakdown," and

Embden (see later) does not consider creatine to be the precursor of ammonia. There is probably no measurable amount of creatinine in living muscles and none appears to be formed in fatigue or even in a few hours' autolysis. In the present state of our knowledge it seems that we must regard the creatine as being in a physiologically reversible equilibrium with the orthophosphate and the phosphagen of the muscle, partaking in no other chemical mechanism.

During such comparatively slight degrees of fatigue as we have been considering there appears to be no breakdown of pyrophosphate, that is, no breakdown which is not immediately and completely reversed after the twitch or tetanus. In long series of twitches, however, Lohmann reports a disappearance of pyrophosphate which he believes to be of the nature of a death change. In a series of 1500 maximal isometric twitches (frog gastrocnemii) some 60 per cent of the pyrophosphate disappeared (76). All this pyrophosphate could be accounted for as orthophosphate, for the proportion of acid-soluble phosphoric esters actually fell slightly. Generally speaking, in his experiments, the sum "ortho- plus pyro- plus phosphagen-P" was practically constant. All observers seem agreed that the total acid-soluble phosphorus remains constant, no matter what treatment is given to the muscle.

STUDIES OF DIFFUSION. The increased blood phosphate concentration and increased excretion of phosphate attending muscular exercise are now explicable without the necessity of postulating any change in the permeability of the muscle cells to phosphorus, if we suppose the observed increase in orthophosphate in the protein-free extracts to mean an increase in the muscle. At the same time an explanation is afforded for a number of other observations hitherto somewhat puzzling. Bearing in mind that inorganic phosphate and creatine can diffuse from muscle tissue into surrounding saline solutions,[3] whilst phosphagen (48) and pyrophosphate (76) are incapable of such diffusion, the following observations are easily understood.

Urano (49) reported in 1906 that the creatine of fresh muscles was non-dialysable but became dialysable when the muscles were incubated. Embden (50) found in 1922 that although resting frog muscles suspended in Ringer's fluid lost inorganic phosphate by diffusion hardly at all, yet when the muscles were stimulated to fatigue a large diffusion could be

[3] Professor Meyerhof informs me that his own experience leads to the conclusion that creatine does not diffuse into or out of a muscle unless the muscle is dead, or has been stimulated to extreme fatigue. In the latter case protein can also "diffuse" to a slight extent, and the muscle is in a pathological state.

observed, and if the muscles were killed (by chloroform) a very rapid diffusion began. It was stated that the diffusion of nitrogen followed much the same course, but Embden did not study this aspect any further. Since Embden had failed to observe any noteworthy increase in the "inorganic" (actually orthophosphate and phosphagen) phosphate content as a result of fatigue he was naturally forced to conclude that the permeability of the cell membranes had been increased. Weiss (51) obtained essentially similar results, and Simon (52) found phosphorus diffusing away from muscles kept in anaerobic Ringer's fluid. Tiegs (53) found in 1925 that the diffusion of creatine followed essentially the same course as had been demonstrated by Embden for inorganic phosphate. He noticed also that if the fatigued muscle were given oxygen the diffusion of creatine was practically stopped. Finally Stella (54) has shown that resting frog muscles suspended in oxygenated Ringer's fluid containing orthophosphate in amount equal to 8 or 10 mgm. per cent P neither lose nor gain phosphate by diffusion: fatigued muscles kept in anaerobic Ringer's fluid require at least twice as much phosphate in the surrounding fluid to maintain an equilibrium. Muscles in rigor were found to be in equilibrium with a Ringer's fluid containing about 100 mgm. per cent P, a figure which agrees well with the inorganic phosphate content as directly estimated (100 to 110 mgm. per cent). The values found by Horton and Eggleton (48) by direct estimation for muscles with which every precaution had been taken to ensure an absolutely resting condition were only slightly higher (12 to 15 mgm. per cent P) than would be expected from Stella's results if his muscles were in simple diffusion equilibrium with the surrounding fluid. But all estimations of the inorganic phosphate content of fatigued muscles give values very much higher than Stella's 20 mgm. per cent—frequently treble that value. It is possible that Stella's muscles were able to recover partially during the somewhat long period (several hours) of immersion in the Ringer's fluid. But it is also possible that some of the orthophosphate found in the acid extract of fatigued muscles is not present in the muscles as such.

MUSCLE PULPS AS ANAEROBIC FERMENTATION SYSTEMS. As in the case of the chemical studies of fatigue and recovery it is difficult to interpret much of the work which has been done on the fermentative processes occurring in minced muscles and muscle extracts. Apart from the difficulty of attaching a meaning to the terms "inorganic phosphate" and "acid-soluble organic phosphate" the situation has been artificially obscured by the misuse of the term "lactacidogen." The confusion arises in this

manner. Embden and his colleagues when studying the production of lactic acid in the juice pressed out of muscle found that glycogen when added to such a juice did not serve as a source of lactic acid (67). The lactic acid which appeared spontaneously in the juice was accompanied by the appearance of inorganic phosphate in amounts which were frequently equimolecular. Embden was led to suppose that the true precursor of lactic acid in these juices (to which he attached the name "lactacidogen") was a hexosediphosphoric ester, and not as had been previously thought glycogen. Hexosediphosphoric ester isolated from yeast fermentation mixtures was found to be glycolysable (100) by muscle juices. Attempts were made to isolate a hexosediphosphoric ester from mammalian skeletal muscle (58) which led to the identification in 1924 by Embden and Zimmerman (1) of a hexosediphosphoric ester which they had isolated, with the hexosediphosphoric ester isolated by Young (115) from yeast fermentation mixtures in 1909. This substance was called "lactacidogen." Meanwhile a method of estimating "lactacidogen" in muscles had been elaborated by Embden's school, which consisted in determining the amount of "inorganic" phosphate liberated when the minced muscle was incubated in a 2 per cent bicarbonate buffer at 44°. It will be observed that a truer name for this fraction would have been "phosphoracidogen," but the assumptions were made, first that this "phosphoracidogen" was a single compound, and second that this compound was the hexosediphosphoric ester which could be isolated from the muscle by suitable chemical treatment. The first of these assumptions was wrong, for it is found that the pyrophosphate in the muscle is the chief constituent of the fraction estimated by the above technique, and the second was wrong, because it is found that resting muscles contain little or no hexosediphosphoric ester. Embden and Zimmerman (4) made this latter discovery and simultaneously showed that resting muscles contain a hexosemonophosphoric ester, to which they transferred the name "lactacidogen." This name therefore appears in the literature with three different meanings, at least two of them wrong.

To avoid misunderstandings I have therefore not used the term "lactacidogen" at all. The fraction of phosphorus compounds estimated by the incubation technique mentioned above is referred to in this review as the "L" fraction. Davenport and Sacks (25) report that the "L" fraction consists of two compounds or groups of compounds, one of which is increased in amount by fatigue, and the other is unchanged. They did not identify any of these compounds. Embden

and Jost (110) found only part of the muscle hexosemonophosphoric ester to be included in the "L" fraction.

For the reasons discussed it is difficult to appraise the value of most of the work published previously to 1927 on the changes occurring in minced muscles and muscle extracts studied as fermentation systems. Ransom (66) in 1910 succeeded in isolating an enzyme system from frog muscle, capable of producing lactate (amongst other things) from glycogen, but he was apparently not interested in the possible significance of phosphate, in spite of the published results of Harden and Young (36) concerning the importance of phosphates in the yeast fermentation. Embden and his pupils began their investigations in 1912, and were soon alive to the possibility of the existence in muscle of a fermentative system resembling that of yeast (68). The finding of Embden, Griesbach and Laquer (100) that yeast hexosediphosphoric ester could be glycolysed by muscle juices was a clear indication in this direction. It was found that the production of lactic acid in the expressed juices of a variety of muscles was always accompanied by the production of phosphate, frequently in equimolecular amounts. The simultaneous breakdown of phosphagen which must have occurred does not affect the validity of their measurements, since it appears in these circumstances to be a separate phenomenon. The breakdown of pyrophosphate now known to occur simultaneously renders it impossible to attach any physical meaning to the equimolecular ratio which was usually, though not always, observed (58). Meyerhof reported in 1917 (69, 71) that a boiled extract of yeast could restore the respiratory function to washed muscle, and that a boiled extract of muscle (and indeed of several other tissues) could act as the co-enzyme to washed yeast. In both cases the activating principle appeared to be thermostable and dialysable. Here was further evidence of a similarity between the two fermentative systems. Embden and his pupils concentrated their attention on the "L" fraction of the muscle phosphorus, showing that it was more abundant in white than in red muscles (101), probably absent from plain muscle (118), diminished in amount by fevers (114), by strychnine poisoning (102) and by muscular fatigue (in rabbits) (102). It was found that generally speaking about one-third of the phosphorus of a skeletal muscle was contained in the "L" fraction. Meyerhof showed in 1921 (127) that in a buffer consisting of isotonic (2.4 per cent) disodium hydrogen phosphate all the carbohydrates of the muscle disappeared (with the production of lactic acid), and even added glycogen was attacked, although this was not the case

if bicarbonate were used as the buffer instead of phosphate. Laquer (70) made almost simultaneously the same observation. Here was a possible explanation of Embden's earlier failure to obtain glycolysis of added glycogen in muscle juices. Indeed in a bicarbonate buffer the muscle pulp stopped glycolysing before its own carbohydrate was used up, though the addition of phosphate at this stage permitted the glycolysis of the remainder. (See also 72, 73.)

An important study was begun by the Embden school of the influence of ions upon the fermentative changes occurring in muscle pulps suspended in buffer solutions; some ions, it was found, accelerated the breakdown changes, others inhibited or even reversed them. Of these the fluoride ion was the most potent and received the greatest share of attention (103, 74, 8, 102). It was found that it caused a disappearance of "inorganic (ortho-) plus phosphagen" phosphorus (using present day terminology) with the formation of "organic plus pyrophosphate" phosphorus (at that time described as "lactacidogen"). Simultaneously a disappearance of lactate seemed to take place (74), though doubt attaches to this observation, for it has been reported by Lipmann (104) that the presence of fluoride interferes with the estimation of lactic acid by the usual method, causing low results. Lipmann, avoiding this source of error never observed any such anaerobic disappearance of lactate. That fluoride does not inhibit the disappearance of glycogen (as was reported by Lange (75)) seems well established (9, 78). It was found by Eggleton and Eggleton (105) that phosphagen disappeared from chopped muscles under the action of fluoride, and in the case of initially resting muscles its disappearance accounted for the whole of the disappearance of "inorganic" phosphorus: that is to say, the true inorganic orthophosphate did not alter in amount. Nevertheless a disappearance of true inorganic phosphate can occur in a muscle pulp incubated in the presence of fluoride, for added phosphate can disappear, and since there is a simultaneous loss of glycogen it would be not unreasonable to suppose that a hexosephosphoric ester accumulates, though it would be rather misleading in this event to refer to it as a "synthetic" process; it would be rather a simple inhibition of glycolysis by the fluoride, such as is familiar in the case of blood. The "fluoride effect" is less marked in the case of fatigued muscles (44, 81, 10, 22), and cannot be observed at all in the case of muscles which have previously been allowed to go into rigor (Deuticke, 79). It has been observed in heart muscle pulps by Perger (83) though not in the stomach muscle of the frog (Eggleton and Eggleton, 56), and no such effect could be

demonstrated by Euler, Myrback and Carlssen (80) in yeast cultures on glucose. Meyerhof and Lohmann find a complete similarity between yeast and voluntary muscle in this respect when glycogen is the source of carbohydrate. Andrews (77) found that the addition of glycogen to the muscle suspension increased the extent of the fluoride effect, a result also reached by Embden and Zimmerman (1) in 1924; addition of phosphate also enhances the effect (Beattie and Milroy, 78). From a large batch of dog muscle which had been incubated in the presence of fluoride and glycogen, Embden and Zimmerman (1) isolated a large quantity of hexosediphosphoric ester which was found to be identical with the diphosphoric ester obtained by Harden and Young from yeast fermentations. This would appear to be the ester which accumulates under the action of fluoride, since these authors have recently failed to find it (4) in perfectly fresh dog muscle (confirmed by Pryde, 2). See also Lipmann (88), and Beattie, Bell and Milroy (113).

CELL-FREE EXTRACTS OF MUSCLE. Meyerhof succeeded in 1925 in simplifying considerably the conditions in which the glycolytic enzyme system of muscle could be studied. He found that the extraction of crushed frog muscle with supercooled isotonic potassium chloride, the extract being separated by rapid centrifugalisation, yielded a solution free from cells or suspended particles and containing little or no carbohydrate, but very rich in glycolytic power. These extracts deteriorated in a few hours even at room temperature. Ultrafiltration separated the ferment system into a heat-stable dialysable fraction (the coferment), and a heat-labile non-dialysable fraction, both fractions incapable of producing glycolysis alone, but reforming the complete enzyme system when remixed. Like Laquer's minced muscles these extracts could glycolyse a number of polysaccharides as well as hexose-di- and mono-phosphoric esters, but were unable to attack glucose and other hexoses. Similar extracts made with distilled water (particularly if prepared from rabbit muscle) were able to attack glucose with great rapidity when quite fresh, though never as rapidly as glycogen.

The rapid deterioration of these extracts leading to a complete loss of ability to glycolyse polysaccharides and hexoses was not evident with regard to their ability to glycolyse hexosediphosphoric ester. The unstable component of the system is clearly not necessary for the glycolysis of this latter. A rabbit muscle extract which through ageing has lost its ability to attack hexoses is renovated by the addition of "yeast activator" (an extract of yeast, soluble in water but precipitated by 50 per cent alcohol). Frog muscle extracts can be made to attack

glucose by addition of the same "activator." In the presence of this activator the muscle extracts can glycolyse hexoses (galactose excepted) even more rapidly than they can glycogen (85). This rapid glycolysis of hexoses was found to be accompanied, not by a production of orthophosphate, but by its disappearance. Only when there was no carbohydrate left, or alternatively no phosphate, did this disappearance of phosphate come to an end, and simultaneously the speed of lactic acid production fell to a low figure. In a case where phosphate and sugar "run out" together two distinct phases in the glycolysis are apparent:

1. Rapid production of lactate with disappearance of equimolecular amount of orthophosphate.

2. Slow production of lactate with reappearance of orthophosphate in equimolecular amount.

Phase (2) presumably begins soon after phase (1), but its relative slowness is such that it has hardly got under way by the time phase (1) is finished. Hence the possibility of distinguishing them. These muscle extracts have been found to contain usually only a trace of phosphagen; any that is present initially rapidly disappears from the untreated extract with no production of lactic acid, and added creatine-phosphoric acid behaves similarly. These earlier results, therefore, require no correction on that account, nor, fortunately, does the discovery of pyrophosphate in muscles modify the results, since the amount in these extracts is very small and is practically unchanged in the course of an experiment. It was included in the "preformed ester" phosphorus in Meyerhof's earlier papers.

The relatively simple constitution of his muscle extracts enables Meyerhof to study the "fluoride effect" with greater exactitude than is possible when one is dealing with minced muscle. An extract to which no carbohydrate has been added shows practically no response to the addition of fluoride (82) since it contains practically no carbohydrate. If carbohydrate be added orthophosphate disappears, but very little lactate is formed. The total amount of carbohydrate dealt with in a given time is apparently not altered, for the esterification (judged by the disappearance of phosphate) plus the lactate production is not altered markedly. The fluoride would therefore seem to be inhibiting a breakdown process and revealing, but not accelerating, an esterification process.

The work of Meyer (86) in Meyerhof's laboratory on the purification of the enzyme system concerned in lactic acid production has resulted in the separation of three distinct factors. Repeated precipitation with

acid acetate buffer and subsequent solution in slightly alkaline phosphate buffer results in the removal from the crude muscle extract of a considerable amount of protein impurity together with all the phosphate and the dialysable co-ferment whose nature is unknown, but which can be separated from the phosphate by treatment with barium chloride and colloidal iron. The concentrated enzyme together with the purified co-ferment has no glycolytic power until phosphate is also added. Meyer has recently extended his results (86a) and reports that a twenty-fold concentration of the enzyme is easily obtained and that the purified product is much more stable in solution than in the original muscle extracts. It is also less susceptible to the inhibiting effect of fluoride.

The hexosemonophosphoric esters prepared by Neuberg (108) and by Robison (3) behave very similarly to the hexoses when added to muscle extracts (87). A rapid production of lactic acid accompanied by a disappearance of orthophosphate is followed—as soon as the original ester or the phosphate is used up—by the slow production of lactic acid and the reappearance of phosphate. Though they did not actually isolate it Meyerhof and Lohmann are of the opinion that the ester which accumulates in the first stage is identical with yeast hexosediphosphoric ester, since it shows the same susceptibility to the catalytic effect of arsenates in its glycolysis. Again fluoride inhibits the production of lactic acid and causes an accumulation of the di-ester. The presence of the dialysable co-ferment is necessary for the fermentation of these mono-esters, which therein resemble the polysaccharides and differ from hexosediphosphate. Various synthetic mono-esters were found to be non-fermentable by muscle extracts.

Meyerhof considers that the glycolysis of a hexose in a muscle extract is brought about by the formation of a hexosemonophosphoric ester—not the stable form which has been isolated but a molecule of fleeting existence which rapidly breaks down in the manner expressed by the equation

2 glucose + 2 phosphate → 2 ("nascent") hexosemonophosphoric ester → 1 hexosediphosphoric ester (stable) + 2 lactic acid

The di-ester, though relatively stable, breaks down slowly into lactic acid and phosphate. Arsenates hasten the breakdown of this ester; fluoride and certain other ions inhibit it.

The recent discovery of pyrophosphate in muscle probably does not affect the interpretation of these experiments, for the purified enzyme of

Meyer which is freed from any pyrophosphate originally present, exhibits essentially the same properties as the crude extracts.

PHOSPHATES AND AMMONIA PRODUCTION. Recently Embden and his colleagues have turned their attention to another chemical accompaniment of muscular contraction. It has been known for years that the death of a muscle is accompanied by the production of small quantities of ammonia. Parnas and his co-workers (99) have recently demonstrated a small but quite definite formation of ammonia in frog muscles resulting from injury or fatigue. Embden has brought forward evidence that the ammonia so produced is derived from adenosinephosphoric acid (adenylic acid or adenine nucleotide) by the removal of its amino group leaving inosinic acid (hypoxanthine nucleotide). According to Embden this change is reversible after a contraction to the extent that the ammonia formed can disappear again, though Parnas, and also Nachmansohn (55) deny this. It is not yet known what becomes of this ammonia, supposing that it does disappear. The evidence upon which Embden's thesis is based is not yet very strong. The production and removal of ammonia in fatigue of isolated frog muscles is well established: large individual variations render it unsafe to quote average figures, but it may be said that a resting frog's muscles contain 10 to 20 parts per million of ammonia, an amount which is increased in moderate fatigue (in the isolated muscles) to 30 to 60 parts per million, and in death, or as a result of incubation in a bicarbonate buffer may rise to 200 or 300, which latter quantity probably measures the amount of the precursor in the muscle. If adenylic acid is added to a muscle pulp it gives rise to ammonia to the extent of nearly one-fifth of its nitrogen content (91): so also does adenosine, though adenine is practically untouched. Schmidt (92) records that it is possible to isolate separately from the muscle an adenylic acid deaminase and an adenosine deaminase.

A crucial test of the thesis would be to show the disappearance of adenylic acid and the equivalent appearance of inosinic acid in fatigue. This Embden has not yet attempted, but the following experiment gave results which can be interpreted as a confirmation of the hypothesis. The total nitrogen contained in the Van Slyke copper-lime precipitate from a protein-free extract of a muscle is taken as a measure of the adenylic plus inosinic acids present in the muscle, and together with the preformed ammonia represent the total nitrogen concerned in the ammonia-forming system:

$$1 \text{ adenylic acid} \rightarrow 1 \text{ inosinic acid} + 1 \text{ ammonia}$$

If the companion muscle is incubated in a bicarbonate buffer until the ammonia production is complete, then provided that the precursor is all used up, five times the ammonia nitrogen present at the end of the incubation should also measure the total nitrogen in this system. These two measures were found to agree for muscles in a variety of conditions within a reasonable degree of exactitude (93). It is not claimed that this result affords proof of the thesis, but it is interpreted as a confirmation.[4] Parnas (128) has reported that whilst resting muscles killed rapidly yield 26 mgm. per cent adenine nitrogen and 5 mgm. per cent hypoxanthine nitrogen, if the muscles are killed slowly the figures are practically reversed, and the muscles are considerably richer in ammonia.

Lehnartz has shown that inorganic orthophosphate disappears from a muscle juice buffered with 2 per cent bicarbonate when adenylic acid is added. The disappearance is very rapid and lasts for two or three minutes, showing then a tendency to reversal. His first thought was that hexosemonophosphoric ester was formed (95) but a more exact study (94) showed that pyrophosphate and phosphagen were the products formed at the expense of the orthophosphate. These results promise to be extremely interesting, but it would be premature at this stage to discuss their significance.

Embden considers that the first events to occur in a muscle twitch are the production of ammonia from adenylic acid and the production of orthophosphate from hexosemonophosphoric ester—both changes leading to a decrease in acidity. The production of lactic acid, in his view, follows later (109).

MYOTHERMIC CONSIDERATIONS. The myothermic studies of A. V. Hill, Hartree, and others provide us with practically the only exact data we have concerning the chemical processes accompanying muscular activity and recovery. In themselves they supply no indication of the nature of the substances concerned, but they form a base on which any chemical theories must ultimately fit.

A muscle in performing a single twitch liberates a quantity of heat which is strictly proportional to the tension developed, and the dimensions of the muscle. This heat is the algebraic sum of the heats of all the chemical reactions and physical changes involved in the twitch. The balance is exothermic: at no stage in the performance of the twitch

[4] Any creatinephosphoric acid in the protein-free extracts would be included in the copper-lime precipitate and cause an error, but this possibility was avoided by allowing the acid extracts to stand for some hours.

or the subsequent recovery of the muscle is there ever a preponderance of endothermic reactions. Two sets of reactions may be distinguished:

a. Reactions inevitably associated with the performance of the twitch: these occur in the complete absence of molecular oxygen and are completed in a few seconds.

b. A set of reactions which can only occur in the presence of molecular oxygen and which may be dissociated from the first set by excluding oxygen until several minutes after the twitch.

The two sets of reactions have almost equal thermal values, the second being slightly greater.

It is impossible to determine directly the chemical changes accompanying a single twitch but fortunately the facts summarised above apply equally to a succession of twitches. Meyerhof has studied in detail the lactic acid production in successions of twitches and it is possible to make an important generalisation (see A. V. Hill, 84) connecting the mechanical, thermal and chemical responses occurring in isometric conditions in the absence of molecular oxygen, viz.,

$$1 \text{ gm. cm. of heat} \equiv 5.9 \text{ gm. cm. of tension-length} \equiv 6.1 \times 10^{-5} \text{ mgm. of lactic acid formation}$$

"Tension-length" is the product of the tension produced in a twitch and the length of the muscle. It has the dimensions of energy (ML^2T^{-2}) and might be expected to measure the energy output of the muscle in the twitch. Actually, as the equation indicates, the energy output is 17 per cent of this quantity (1/5.9).

There are two important limitations to the validity of these relationships. The applied stimulations must not be supermaximal, and the muscle must not be in a fatigued condition. The numerical values given apply to the sartorius of the frog. It is very probable that the lactic acid production together with its subsequent neutralisation, accounts for almost all the observed heat production, but for the present purpose it does not matter what is the thermal value of the remaining chemical processes; the important thing is that such of these remaining reactions as have any considerable thermal accompaniment must also be proportional in extent to the total tension-length.

The production of orthophosphate is one of these remaining chemical reactions, but it is not proportional in extent to any of the factors considered above. This was shown by Nachmansohn (55), who compared the "phosphagen breakdown" in a series of twitches with the lactic acid production and the sum of the tension-lengths, and entirely

comparable results have been obtained in this laboratory. It follows, either that the thermal value of this reaction is negligible, or that its heat production is exactly counterbalanced by some endothermic chemical reaction. The former alternative is more credible, but this means that the "breakdown of phosphagen" in the muscle is not synonymous with the "hydrolysis of creatinephosphoric acid" in vitro, for the latter reaction has a considerable heat value, about 11,000 calories being liberated per gram molecule of phosphoric acid. Moreover the "anaerobic resynthesis" of phosphagen which has been observed would be a powerful endothermic reaction, and is not balanced by any known exothermic processes in the muscle.

It seems simpler to suppose with Nachmansohn, and Hill (84), that this "breakdown of phosphagen" is not a hydrolysis of creatinephosphoric acid into stable creatine and orthophosphate although it appears to be such when protein-free extracts of the muscle are analysed.

INVERTEBRATES. Meyerhof (112) has found that the muscles of several genera of invertebrates contain an "arginine-phosphagen" instead of the creatine derivative characteristic of vertebrate skeletal muscle. It may be also that insects use this arginine complex, for Irving and Wells (41) failed to find evidence of the presence of the vertebrate type in the legs of grasshoppers (but as they also failed to observe it in fish muscles, the point must be considered unsettled). Meyerhof and Lohmann have studied certain chemical properties of the argininephosphoric acid which they have isolated from crab muscles, but so far not much information is available as to its physiological behaviour. So far as the evidence goes (7) it would seem to resemble its "vertebrate" analogue.

Lohmann has isolated pyrophosphate from the muscles of crabs.

SUMMARY

In order to summarise the present trend of opinion concerning the function of the phosphorus derivatives so far studied in muscle it is convenient to consider them one by one.

Orthophosphoric acid is present in quite small amounts in the different types of muscle which have been examined—probably not in higher concentration than in the fluids surrounding the muscle. It must exist in the resting muscle mainly as the secondary salt and therefore must exert a buffering action against the production of acidity. If any is liberated in exercise from phosphoric esters (which is doubtful, unless a severe oxygen debt is incurred) a further buffering effect would be

exerted, because phosphoric esters in general are stronger acids than orthophosphoric acid (i.e., R-$KHPO_4$ is more acid than KH_2PO_4, and R-K_2PO_4 is less alkaline than K_2HPO_4), but it appears that the muscle proteins form the chief source of buffering power.

Phosphagen is clearly an "adjunct" evolved by the more highly specialised types of muscle, which are characterised by rapidity of contraction and by entire lack of autonomy.[5] It is a useful working hypothesis to suppose that it is concerned in the translation of nervous impulses into mechanical response, and it is possible also that it may be a source of phosphate more readily available for esterification of carbohydrate than free orthophosphate. Fiske (5) has pointed out that the hydrolysis of creatinephosphoric acid would provide an accessory buffering system for the muscle, since it is a stronger acid than orthophosphoric, but it is not at all certain that this reaction ever occurs in a muscle.

It is a very significant fact that the "phosphagen" of invertebrates contains arginine in the place of creatine. Since creatine has never been isolated from the tissues of invertebrates it appears likely that it has no function in vertebrates apart from its connection with the phosphagen complex. One is tempted, too, to speculate upon the possibilities of "chemical evolution" opened up by these discoveries. Phosphagen of the vertebrate type has been reported by Eggleton and Eggleton (105) in the primitive marine vertebrate *amphioxus*, and Meyerhof (112) has confirmed this, estimating both creatine and phosphorus. The introduction of a new chemical compound into the chemical arrangements of a tissue is a form of evolution which necessarily must occur as a "mutation"—a molecule cannot be incorporated by degrees.

Hexosemonophosphoric ester is present in frog gastrocnemii to the extent of about 0.05 per cent (rabbit muscles are considerably richer according to Lohmann), and to judge by the results of fermentation studies on muscle extracts, it is quite likely to be the immediate precursor of lactic acid in muscular contraction. But practically nothing is known directly of its behaviour in intact muscles.

Hexosediphosphoric ester is probably absent from muscles under normal conditions but tends to be formed in abnormal circumstances, as when the muscle is minced and incubated in the presence of fluoride, or when the muscle juice ferments carbohydrates. There is no direct evidence of its appearance in intact muscles. The function of both

[5] Cardiac muscle is apparently in an intermediate position.

hexosephosphates in muscle is probably akin to their function in the yeast fermentation. Neither problem is yet solved.

Pyrophosphoric acid in muscles has not yet been studied sufficiently for any theory to be formed as to its significance. Muscles are not peculiar in containing it, for Lohmann (107) has isolated it from yeast, and found evidence of its presence in a variety of tissues, and in certain bacteria. A pyrophosphatase is also common to a number of animal tissues (Kay, 111), and Lohmann has tentatively expressed the view that it is concerned primarily in cell respiration. Its chief claim to importance at present is the very practical one that it must be allowed for in estimates of the "organic phosphorus" of muscles. The older estimates are, for the moment, meaningless.

Adenylic and *inosinic acids.* The former has been found in fresh muscles, and the latter has long been known as a constituent of meat extracts. Embden links them together to account for the production of ammonia which occurs in fatigue or in death (inosinic acid being deaminated adenylic acid). Muscles appear to contain an adenylic acid deaminase. Their interest at present however lies not in their being phosphoric esters, but in their possible significance in purine metabolism.

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ON CEREBRAL LOCALIZATION

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The problem of cerebral localization as seen by the clinical neurologist is confined almost entirely to discussion of localization in that portion of the cerebral hemispheres which the comparative neurologist calls the neopallium. And in such a discussion the significance given to the word localization, itself, is so important an indicator that if the observer's definition be known, the interpretation of the findings may be predicted by an unprejudiced reader. Probably in no other field of neurology does the affective quality of what masquerades as logic appear in such gorgeous costume. For this reason, and another, namely, that the present meaning of the word localization for the cortex cerebri has been rather adequately delimited by both Head and Goldstein, the reviewer wishes to approach the consideration of this fascinating problem not by the historical high road, but rather by the devious and somewhat isolated pathway of comparative neurology.

The analysis developed in this field is based upon laborious classification of areas of the brain, according to their neuronic connections. By tracing a chain of neurones from a primary receptive field to the terminus, a functional system based upon relation to the peripheral end organ is isolated. Regions of the brain are thus differentiated by the source of the axis cylinders they receive, and by the locus of termination into which their intrinsic perikaryons discharge. Such a method is not above criticism. Nevertheless, it has a contribution to offer. Related to this type of analysis is that of the embryologist, who follows the development, maturation and differentiation of areas within the cerebral hemisphere. Such data strengthen the all too slender wall of deductions from comparative neurology with an occasional buttress. These analyses, together with the data furnished by the student of the cyto-architecture of the cerebral cortex, cast an uncertain light upon the observations of the physiologist. Knowledge of all these types of approach to the general problem furnishes a rather necessary background for the understanding of the action of such a complex structure as that of the cerebral cortex.

The comparative neurology of the telencephalon. In the almost entirely unevaginated telencephalon of fish (Johnston, 1898, 1901, 1902, 1906, 1911, 1912; Holmgren, 1920; Kappers, 1906; Herrick, 1922) there is little of apparent resemblance to the same division of the brain in higher vertebrates. However, five areas stand out, differentiated by their fiber connections. The *area olfactoria medialis* lies immediately cephalward of the region known in higher brains as the nucleus preopticus, and receives fibers not only from the evaginated part of the telencephalon (the olfactory bulb) but also from the hypothalamus. Since the hypothalamus receives fibers from the gustatory centers lying caudalward, this area may be thought to be a correlation center. These three regions, lying in a continuous column, are connected by a tract of ascending and descending fibers, the medial forebrain bundle,—a relationship of nuclei and tracts which is characteristic of all vertebrates.

The area olfactoria dorsalis lies immediately posterior to the bulbus olfactorius and is connected with that epithalamic nucleus, the habenula, by a largely efferent system, the stria medullaris thalami, and with the hypothalamus by a complex of fibers, the tractus pallii. The *area olfactoria lateralis* is bounded by the area olfactoria dorsalis, the bulbus olfactoria, and the anterior commissure, and receives fibers from the tractus olfactorius. The remaining two areas, olfacto-somatica and somatica, to use Herrick's nomenclature (1922), are connected with the thalamus proper, by both ascending and descending fibers. The first of these, although it may have no terminals from the tractus olfactorius, is closely related to the area olfactoria dorsalis by short neurones. The ascending fibers which enter the area somatica originate in the afferent centers of the thalamus, and the descending fibers discharge into the ventral efferent portion of the diencephalon. Of this simplified and little modified form of telencephalon, Acipenser may be taken as the type for comparing the brains of other fishes.

The evaginated portion of the telencephalon of the lamprey, Ichthyomyzon concolor (Herrick and Obenchain, 1913), contains the olfactory bulb and part of a secondary olfactory area, homologous perhaps with the area olfactoria lateralis. The large area olfactoria dorsalis lies in the telencephalon medium dorsal to the foramen of Monro. Ventral to it is a region called the lobus subhippocampi, continuous cephalward with the evaginated lateral olfactory area. Ventral again lies a region homologous with Acipenser's area somatica, the primordium of the corpus striatum. Certainly this region receives fibers from the thalamus, which constitute the tractus strio-thalamicus. And again ventral

to this "striatum" are the area olfactoria medialis and the nucleus preopticus; lying, therefore, in the telencephalon medium below the foramen.

In the elasmobranch, Squalus acanthus (dog-fish), there is a partial evagination of the rostral end of the telencephalon following the wide, lateral outgrowths of the olfactory bulbs. The caudal portion remains in the telencephalon medium,—that is, the areae olfactoriae have evaginated, leaving behind the non-olfactory regions. And a new nucleus, lying in close relationship to the lateral and medial olfactory areas has appeared, the tuberculum olfactorium. The dorsal olfactory region, (primordium hippocampi, of Johnston) has advanced slightly toward the cortical type of higher vertebrates, and is separated from the underlying area medialis by a cell-free zone, a characteristic of the telencephalon of amphibians and reptiles, and found, as well, during development of the homologous region in mammals. The connections of all these differentiated parts are similar in outline to those of Acipenser. The medial part of the dorsal olfactory area, moreover, is connected with the hypothalamus, forming a primitive fornix. The lateral part, only, is joined by the tractus pallii to the hypothalamus. These fiber connections might be interpreted as demonstrating this total dorsal olfactory area to be the anlage of the lobus pyriformis and the hippocampus.

The departure from the type set by Acipenser found in the teleosts, adds little to the understanding of the phylogeny of the telencephalon. The dorsal olfactory area shows the most marked differentiation, but not one in the direction of cortex formation, although it is apparently the anlage for the archipallium.

The telencephalon of fishes may then be divided into five areas, three olfactory, one olfacto-non-olfactory and one definitely somatic. The more dorsal of these olfactory nuclei is connected with the habenula and, in the dog-fish, with the hypothalamus; the more ventral or medial, with the hypothalamus; the lateral, with the olfactory bulb; and the olfacto-somatic and the somatic with the thalamus.

A glance at a transverse section of the telencephalon of an amphibian, be it frog or amblystoma, taken anterior to the foramen interventriculare (of Monro), reveals the quadrant division of Herrick (1910) as inherent in the material. The dorsal and ventral divisions of the medial half are separated not only by a deep ventricular groove but also by the cell-free zona limitans media. Both the dorso-medial and ventro-medial divisions are again delimited from the dorso-lateral and ventro-lateral regions, respectively, by deep ventricular grooves. Another such sculpturing on the inner surface of the lateral wall separates its dorsal and ventral moities.

The dorso-medial sector is the primordium hippocampi. It receives fibers from the olfactory bulb and from the ventro-medial sector, and sends fibers into the hypothalamus via the fornix. Further, it is correlated with the dorso-lateral area, the lobus pyriformis, by fibers running through the nervous tissue and forming the vault of the telencephalon. The ventro-medial region is called septum by the majority of American comparative neurologists. It is rather unambiguously homologous with the area olfactoria medialis of fishes. At no time does this region show any cortical characters. It remains as one of the basal secondary olfactory areas throughout the vertebrate series. The ventro-lateral sector is related to the thalamus, and, via the olfactory projection tract, with the hypothalamus: the anlage, then, of the corpus striatum complex. The dorso-lateral quadrant, the lobus pyriformis, receives many secondary olfactory fibers, is related by fibers to the thalamus, and retains the tractus pallii connections of this region in fishes. It therefore combines certain characters of the areae olfactoriae dorsalis and lateralis as well as those of the area somatica of fishes. There is, then, no area in the amphibian hemisphere which may be regarded as neopallium, nor even for that matter, as its primordium. And although the dorso-medial wall is the anlage of the hippocampus, it is doubtful whether or not it has a true cortical structure, although Kappers (1928) refers to that region in the frog as archicortex, and the dorso-lateral sector in the same amphibian as paleocortex.

Marked differences are apparent in a similar transverse section through the brain of a reptile. Within the ventro-medial quadrant, the septal region of Herrick (1910) and Hines (1923), the separate groups of nuclei may be seen, which remain rather constantly throughout the lower mammals, such as the monotremes and marsupials, and in the embryonic stages of man (Hines, 1922). The ventro-lateral sector, now comprising the greater bulk of the tissue of the whole telencephalon, contains what all agree to be the older part of the corpus striatum, which is closely connected with the hypothalamus. The exact homologies are as yet amorphous.

The plane of division between the ventro-lateral and dorso-lateral sector cannot be passed with the decision characteristic of this region in amphibians, except in the embryo. In the developing telencephalon of the turtle (Johnston, 1916), and of Sphenodon punctatum (Hines, 1923) there is a prominent ventricular groove, disappearing in the adult, yet delimiting the two lateral sectors before maturation. The more dorsal can be seen to contain that tissue which later develops into the

dorsal ventricular ridge of Johnston (1915, 1916), the hypopallium of Elliot Smith (1919), the neostriatum of Kappers (1908) and Hines (1923) or the dorso-lateral area of Crosby (1917). To discuss its mode of origin is beyond the scope of this paper. Lateral to it, at the cephalward part of the telencephalic vesicle, lies the nucleus olfactorius lateralis; its middle division bounds the lobus pyriformis, and its caudal, the nucleus which is homologous with the amygdala of mammals. The structure itself is related to the thalamus by strio-thalamic and thalamostriate fibers, the lateral forebrain bundle (Johnston, 1915; Crosby, 1917; de Lange, 1911; Hines, 1923; Cairney, 1926). The amygdaloid component already possesses the more fundamental of the mammalian connections. It sends fibers to the habenula (stria medullaris, Johnston and Crosby), to the medial olfactory centers via the stria terminalis, and the hypothalamus: the olfactory projection tract. The ventral sectors, therefore, disregarding the lobus pyriformis, might be said to be homologous to the medial or subcortical olfactory centers, and the ventro-lateral plus the medial part of the dorso-lateral to the basal ganglia of the mammalian telencephalon. It is rather the dorso-medial region and the dorso-lateral, minus its striatal component, which are of immediate interest for this review.

The dorso-medial quadrant contains the archicortex or hippocampus. The receptive cells, which are granular, are interpreted on the one hand as cells characteristic of the hippocampal cortex, and again by others, as the receptive layer of the fascia dentata (de Lange, 1911; Meyer, 1892; Kappers, 1921). The cortex lying lateral to this in the vault of the hemisphere is made up of small pyramids, and all agree that it is, indeed, hippocampus. The whole area is connected afferently and efferently with the septum, and, generally speaking, with the hypothalamus,— fiber relationships which are characteristic of certain fishes, amphibians and mammals. It sends tangential fibers laterally to a narrow regional differentiation in the vault, thought to be general cortex (Kappers, 1921, snakes; Johnston, 1915, turtles; Crosby, 1917, alligator).

Laterally lies the paleo-pallium, the lobus pyriformis. It is connected with the lateral olfactory tract and nucleus; with the underlying striatum, and probably, also, with the medially lying general pallium.

Primitive general cortex lies, therefore, between the archipallium or hippocampus medially and the paleopallium (or lobus pyriformis), laterally. Cairney (1926) found in Sphendodon punctatum, an archaic reptile, only slight evidence of somatic connections to the dorsal general

cortex, and then only in its more rostral part. In the main, the general pallium of this reptile is, apparently, an association area interposed between the hippocampus and the lobus pyriformis. It has been interpreted both as a sensory projection area and as a correlation center for the older cortical regions. The somatic connections of the general pallium are with the dorsal small-celled area of the striatum. It is not related directly, either afferently or efferently, to the thalamus. The type of function which Herrick suggests this fiber to carry into the general pallium is that of general cutaneous sensibility, transmitted from the lateral and medial nuclei of the thalamus to that part of the striatal complex which underlies the area of general cortex. Upon the basis of fiber connections, Crosby distinguishes three types of cortical centers: the hippocampus, an olfactory receptive center, concerned mainly with olfacto-visceral correlations; the lobus pyriformis, concerned chiefly with olfacto-somatic correlations, with some relationship to the hypothalamus; and a third type, the general cortex, receiving incoming somatic impulses from the thalamus via the "corpus striatum." Apparently here, also, fiber connections are present which would allow correlation of this type of impulse with those received by the hippocampus and pyriform lobe.

This general pallium, represented in reptiles by a few cells, acquires dominance in the higher mammalian cortices. It is for this portion of the cortex cerebri, in laboratory animals and in man, that we will discuss the problem of localization. The pallium of the bird contributes little to this type of analysis, possibly because of the specialization of these forms away from the vertebrate stem. And at the present time, there is no known connection which can account for the definite results of electric stimulation of the pigeon's thin cortical mantle recorded by Rogers (1922).

Embryological development of the telencephalon. In the developing telencephalon of Sphenodon (Hines, 1923), of the turtle (Johnston, 1916) or of man (Hines, 1922) the cortex which first delimits itself by peculiar arrangement of neuroblasts, is the hippocampus. This process is followed closely by the separation of cells away from the dorsal ridge of the striatal complex to the anlage of the lobus pyriformis. Between the dorsal limits of these two formations lies the undifferentiated neopallium. The difference in the amount of this tissue in the two reptilian brains and in that of man is striking, and becomes increasingly so in older stages of development. The primordium of the hippocampus changes in position from forming the dorsal part of the telencephalic

arch (11.8 mm. human embryo, Hines, 1922) to forming its dorso-medial wall (14 mm. human embryo). And the amount of neo-pallium is greater at this stage at the anterior pole than at the posterior. As the process of development continues, the hippocampal formation comes to lie entirely within the medial wall. The neo-pallium then apparently grows greatly in the posterior pole, and the hippocampus makes, simultaneously, the ventro-caudal turn so characteristic of it. Such a study gives some data concerning the regional acceleration of neopallial growth; the acceleration seems to shift from the frontal to the dorsal, then to the posterior poles of the developing hemisphere, and, finally, back to the frontal.

Concomitant with this change in position, proceeds intrinsic differentiation within the hippocampus. Although set aside as the first delimited cortical area, differentiation progresses so slowly that such cell layers as are characteristic develop in the neopallium long before they are complete in the hippocampus itself. The cell laminations in different parts of the neopallium of the oldest human embryo studied (40 mm.) are not characterized by a difference in number, but rather by a difference in the relative distribution of neuroblasts within them. The outer cell layer, called the pyramidal layer, is separated from the outer limiting membrane by a cell-free zone varying in thickness, and, again, from the intermediate cell layer by a deeper cell-free zone. The intermediate cell layer is directly continuous with the matrix. The varying thickness of the hemisphere is contingent on differences in thickness of the three cell layers and their separating cell-free zones.

There is no study of cortical lamination for stages of development between those of the author, here presented, and those of Bolton (1910), whose youngest human brain was that of a four month fetus. Bolton has considered the development of three different regions, the prefrontal, the visuo-sensory (often called the sight projection area) and a contiguous region which he has designated the visuo-association area. In some of his fetuses the pre- and postcentral gyri were also studied. The prefrontal cortex of a four months fetus consists of a layer of apparently undifferentiated neuroblasts covered by a zone practically free of nerve cells. He finds all the neuroblasts equally embryonic. At six months definite lamination appears. An innermost cell layer becomes sequestrated by an inner fiber lamina. Both the inner and outer cellular layers exhibit a certain columnar arrangement of neuroblasts. The eight month fetus not only shows the adult demarcation into cortical lobes but also the completion of adult fissuration. Cell

lamination is complete, but the outer or pyramidal cell layer is only about one-half the thickness of the normal adult. The two inner cellular zones approach rather more closely the normal adult thickness. And even at birth, a similar discrepancy in development in the three primary cellular layers is present.

Three months after birth, according to Bolton, the depth of each of the three cell-laminae more closely approximates that of the adult in the visuo-sensory cortex than in the visuo-psychic. With Moyes, he found that the pre- and postcentral cortices, and the visuo-sensory area possess the adult relationship to the central and calcarine fissures. The Betz cells in the precentral region are well developed and, although the visuo-sensory area can be delimited, differentiation is not advanced as far as in the motor cortex. The prefrontal cortex, as might be anticipated, is extremely embryonic. Bolton regards as proven that the pre- and, he adds, the postcentral cortices are developed before the visuo-sensory; that the visuo-sensory develops before the visuo-psychic; and all four before the prefrontal area.

Were such time-consuming studies of the development of cell lamination pushed to the full extent inherent in the material, undoubtedly subtle differences in intrinsic differentiation of cortical areas would emerge; differences which the comparative neurologist might foretell, but which in the time sequence of their emergence might depart from the schedule of phylogeny. But what light can genetic differentiation throw upon regional function in the adult neopallium?

The cyto-architecture of the cortex cerebri. Variety of lamination is a characteristic feature of the cerebral cortex. For several hours after death, more than thirty types of cortex may be distinguished on the basis of the obvious macroscopic arrangement of cell and fiber layers. Elliot Smith (1907) claims that the cortical areas thus grossly established bear such precise relations to the more stable sulci that it is, perhaps, justifiable to consider them as definite units.

Comparison of the cortical map made in this manner by Elliot Smith with those of the more time-consuming studies of Campbell (1905), Brodmann (1909), or Economo and Koskinas (1925) demonstrates certain similarities. The regions known as projection areas bear approximately the same relationship to nearby fissures. The central fissure (Rolando), dividing the precentral gyrus from the postcentral, also marks a transition in cellular lamination. The superior temporal gyrus, by Smith's and Campbell's studies, is of one design; Brodmann and Economo and Koskinas discriminate three concentric fields of

slightly different architecture. All four reports assign approximately the same limits not only upon the mesial surface but also upon the lateral, to a region of homogeneous structure surrounding the visual cortex, (the visuo-psychic area of Campbell and Bolton). That is, on the extent of those areas which have well defined subcortical relationships these four investigators agree. The supra-marginal and angular gyri have similar limits in all the cortical maps except that given by Campbell, who finds a cell structure common not only to them but to the middle temporal convolution also. Again, the boundaries assigned to the three divisions of the inferior frontal convolution differ slightly, but always in what appears to be the same direction. The greatest disagreement is seen in the mapping of the middle and inferior temporal convolutions, the superior parietal lobule and the prefrontal cortex. Bolton found so much individual variation in the development of the latter that he gave up the attempt to follow it beyond three months of age. It is possible, certainly, that the discrepancy in detail of Brodmann and Economo and Koskinas expresses the individuality of the cortices which they studied. Similar variation may be seen in the external configuration of brains used for study in any class room; the main sulci and gyri are present, but with small modifications.

After a careful consideration of the several studies upon cell lamination in the cerebral cortex of man, that of Brodmann appears to have caught more clearly than either that of Mott, Bolton, Campbell or Cajal, the inherent plan of architecture. In many parts, the conspicuous pyramidal cells seem to be separated into two layers by small stellate cells, the lamina granularis interna, layer IV of Brodmann. Those lying above are often grouped as supragranular; those below, as infragranular. The supragranular pyramids form themselves into two distinct zones, an outer or small pyramids (lamina granularis externa), II of Brodmann; and an inner, of medium sized and large pyramids (lamina pyramidalis), Brodmann's III layer. The outer lamina of the infragranular group V contains large pyramidal cells. The giant pyramidal Betz cells of the motor cortex, the origin of the cortico-spinal tract, are found here (lamina ganglionaris). The apical dendrites of these cells are very long and penetrate the superficial zone. Among them smaller pyramidal cells and others of the short axone type are found. Below this layer V lie polymorphic cells in layer VI (lamina multiformis). Layer I, called molecular (lamina zonalis), consists of a band of superficial tangential fibers, with a few nerve cells lying among many neuroglia. These cells are Cajal's horizontal cells and type II of Golgi.

The second important fiber stratum is found in layer IV, and the third in V. The outer half of the deep molecular layer beneath layer VI contains many tangential fibers. The horizontal fibers of the inner half of this layer merge imperceptibly with the central white matter of the hemisphere.

Economo and Koskinas have followed this classification of Brodmann. Further, they have divided the cortex into five types, using the variations on this scheme as classifying characteristics, as follows:

1. The agranular pyramidal type; thick; containing large pyramidal cells, and no (or a negligible) layer IV: found in the prefrontal convolution and the adjacent frontal gyri, and, peculiarly enough, in the limbic lobe.
2. The granular pyramidal type; moderately thick; with prominent pyramidal cells and a broad granular layer (IV). It is seen in the frontal lobe anterior to type 1, in the postcentral gyrus, the superior parietal lobe and in the posterior part of the gyrus cinguli.
3. The granular parietal type; a cortex of medium thickness containing many granular cells. It is found in the inferior parietal lobe, the gyri angularis and supramarginalis, the anterior part of the second frontal convolution, posterior part of the Island of Reil, the major part of the superior temporal gyrus and the gyrus fusiformis.
4. The polar type, a thin cortex, rich in granular cells. It is found in basal and medial part of the orbital gyri of the frontal lobe and in the cuneus and lingual gyrus of the occipital pole.
5. The granular type; distinguished by small cells in all its layers. It is a thin cortex with thick layers of cortici-petal fibers. The inrolled part of the postcentral gyrus, Heschl's convolution and the sight projection are its special examples. Besides these, Economo and Koskinas include the retro-splenial region and the inner wall of the gyrus hippocampus.

Brodmann has designated the histologically distinct areas of the cerebral cortex by numbers, Economo and Koskinas, by letters: for example, Brodmann called the motor cortex, field 4 and the visual sensory area, field 17; on the other hand these regions in the latters' nomenclature are known as Fa and Oc.

Goldstein (1927) would consider cyto-architectural differentiation as having physiological meaning. The agranular pyramidal cortex of the motor area and of the frontal lobe adjacent to it suggests a related func-

tion by this similar arrangement which, in the case of the former, always underlies those areas from which an electric stimulus produces movement and in the latter, may be correlated with facilitation of the motor cortex. But why is this cortex present also in the gyrus limbicus? The granular pyramidal type corresponds loosely, excepting the gyrus cinguli, to those regions from which von Monakow thinks the cortico-pontal fibers arise. And the granular type, with the exception of the retro-splenial region and the inner wall of the gyrus hippocampus which is subiculum, is characteristic of certain of the so-called sensory projection areas. It is difficult to suggest function for the remaining two varieties.

The characteristic distribution of the granular layer in the primary sensory receptive fields suggests the possibility that the granule-cell is indeed the ancient receptive cell. Kappers (1928) finds in serpents and lizards that the olfactory fibers reach the archicortex to end about cells of a granular type. These cells have short neurites which extend to the mantle where the ascending neurones run, and transmit the impulses to neighboring structures only. The cells of the dorsal cortex are pyramidal. They have large neurites which pass into the lining of the ventricle, and enter the hemisphere of the opposite side as commissural fibers, or pass to the hypothalamus and epithalamus as cortici-fugal tracts.

Further, Kappers (1909) believes that a definite evolution of cellular types may be traced in the phylogenetic development of the archicortex. The primary prevailing granular layer in the hippocampus of reptiles gives place in the lower mammalia to an increase of pyramidal cells whose axones are so arranged that they serve projection and bilateral association. The latter are the subgranular pyramids of the ammon formation. In the next stage of development, an "olfacto-psychic" or association center appears, concomitant with an increase in the number of sub-granular pyramidal cells; and within the primary cortical olfactory area supragranular pyramids may be seen, reaching up to the molecular layer. The coincidence of this development makes one think that a certain interdependence may exist between the supragranular pyramids and the olfactory association area,—a sort of inter-regional association.

This study of Kappers was evidently stimulated by a rather complete investigation made by Mott (1907) upon the evolution of the visual cortex in mammalia. Where vision is rudimentary (mole and shrew) the sight cortex consists almost entirely of small stellate cells, which look like granules. Below these is a thin layer of polymorphous cells

and occasional larger pyramids. In the rodents (rabbit and guinea pig) where eyes are set laterally (panoramic vision), he found large stellate cells and branching pyramids lying closely in a thin zone above the granular layer. The sub-granular layers are not well delimited and are composed of polymorphous and some pyramidal-like cells.

As representative of the marsupialia, Mott studied the Wallaby and Dasyuras. The pyramidal layer in the Wallaby, a herbivorous animal, is poorly represented when compared with the well defined supragranular pyramidal lamina of Dasyuras, a carnivorous marsupial. Gray (1924) found that the cortical lamination in the area striata of the opossum (Brodmann's area 17), is characterized by a great development of layer IV, consisting of closely crowded granules. The pyramids in layer V are smaller and less distinct than in the area peri-striata. In the kangaroo (Macropus dorsalis), Brodmann (1909) discriminated three distinct zones in the IV layer. The V had few pyramidal cells, and the VI was filled with large polymorphous and small pyramidal cells. Its supragranular layers, as well as the total laminations of the peristriate region, were more highly differentiated than either in the opossum. Apparently, aside from the Primates, as great variations may be seen in the Marsupials as are found in the Eutheria.

In the Ungulates which were chosen for study by Mott (pig, camel, and muledeer), the supragranular pyramids were not as well developed as the granular or infragranular lamina. In the Carnivora (cat and dog), the evident feature is the relatively greater depth of the supragranular and granular layers compared with the infragranular, which is characterized by many polymorphous cells. With a glance at Mott's figures of the area striata in Macacus rhesus and man, one sees immediately not only a marked increase in the relative thickness of the supragranular layers but also a subdivision of Brodmann's pyramidal (V) and polymorphous (VI) layers; although distinctly differentiated, they are not relatively as thick as the same region in the muledeer, for example. Circumjacent to the visual sensory-cortex lies the visuo-psychic. This cortex is well developed in Macacus and compares favorably with that of man. Peculiarly enough this region was not studied microscopically in the chimpanzee by Mott, although a figure of a gross area is given.

Mott's work may be summarized as follows: In the less developed visual cortices, although the granules still predominate, all layers are poorly differentiated. In the Ungulates, notwithstanding the appearance of supragranular pyramids, the large pyramidal and polymorphous cells which constitute layers V and VI are more numerous. Finally,

when the eyes assume forward direction, in the Carnivora, monkeys and primates, and convergence becomes possible, together with greater independence of eye movement, not only do the supragranular layers, II and III, become thicker, but also there are proliferation and stratification in the receptive granular layer itself. This change seems to be concomitant with increase in the number of uncrossed fibers in the optic tract. Kleist (1926) thinks that the deeper granular lamina (IVc) receives the crossed, and the outer (IVa), the uncrossed fibers. Concomitant with the development of the visual cortex the association region surrounding the visual projection area enlarges and differentiates. Interesting and warranted as these conclusions are, the detail of microscopical study is meagre and incomplete when compared with that of more recent savants, such as Brodmann. Certainly a study of this region in the anthropoid apes, supplementing that of Campbell, is indicated.

Bolton (1914) has compared the actual depths of the outer and inner laminae in the motor cortex in the dog, Macacus rhesus, and man. The outer cell layers in the dog are one-half the depth of these in the ape, and the ape's three-fourths of the depth of man. The layers V and VI are practically the same in Macacus and man, and one-fourth deeper in the dog than in the other two. The ratio of depth of the outer three layers to the inner two is, in the dog, 1:3; in the monkey, 1:1; and in man 4:3. Such intrinsic relations of lamina are probably not unimportant when injuries to this region in these three animals are to be compared.

Van't Hoog (1920) studied the area postcentralis in small and large animals of the same species. The larger animals without exception owned a greater depth of cortex. This increase was not distributed in the infragranular, nor in the granular, but always in the supragranular laminae. In fact, in those which he happened to study, there was an actual decrease in the thickness of layer IV in the larger animals. He believes that the increase in layers II and III happens at the expense of the lamina granularis interna. Comparing his figures for specific total depths of the postcentral gyrus in man, Macacus cynomolgus and the chimpanzee (Troglodytes niger), this cortex in apes is thicker than in man. And although II and III are negligibly thicker than in man, and the lamina granularis (IV) is approximately 40 per cent thinner in the chimpanzee, the sum of V and VI is 37 per cent thicker. Comparatively speaking, then, the ratio of the supragranular layers to the infragranular in the chimpanzee is 1.1 to 1 and in man 1.3 to 1. Relatively,

the supragranular layers compose a greater proportion of the total thickness of the cortex in man, than in the chimpanzee studied. The comparison, it must be acknowledged, favors, but does not establish Van't Hoog's belief that the III layer may develop at the expense of the IV.

THE MOTOR CORTEX. Certainly there is some relation between localized differentiation in the cerebral cortex and the development of certain functions. But just how far that relationship may be pushed and still yield justifiable conclusions the writer does not know. Nevertheless the cyto-architecture of specific areas of the cortex should be studied when their function is analyzed.

The most adequate correlation between cyto-architecture and function of the cortex cerebri is allowed by the precentral gyrus. And peculiarly few such studies exist. Nañagas (1922) examined the distribution of the Betz cells in Macacus rhesus. He found that the giant pyramids are limited to the posterior part of the precentral gyrus near the fissure of Rolando. They are largest in the most superior portion of the gyrus, diminishing in size and number inferiorly. The medium-sized Betz cells overlap the field of the giant, spreading forward over the crest of the frontal lobe and in a narrow stream to the superior part of the sulcus precentralis superior. The small sized pyramids of the fifth layer overlap the other two, extending slightly frontalward the projecting lines of the medium-sized Betz cells. The density of the pyramidal cells follows proportionally the changes in number and size of the giant pyramids of the fifth layer. The third layer is thickest along the lip of the precentral gyrus, which borders the central fissure. In the motor cortex of Macacus the larger Betz cells lie in those areas which Grünbaum and Sherrington (1902) charted for this beast as controlling leg, foot and toes.

Such gradation in size of cell of origin of the tractus cortico-spinalis would be explained by Bevan Lewis (1878) that the greater the distance along which a nerve cell has to transmit its energy the larger will that nerve cell be. But Brodmann says that neither length of axones nor body weight can completely account for variations in size, for the Wickelbär (honeybear) whose body weighs 2 kilograms has larger Betz cells in the motor area than has either the Lemur Macaco (2 kgm. body weight) or man (75 kgm.). He considers that the characteristics of cells are dependent also on their intracortical connections, reflecting the total physiology of the area in the particular animal; that fineness of motor coördination and association play a rôle in their differentiation as well as motor power.

Also, Nañagas noticed a slight variation in the extent and density of distribution of the three types of Betz cells in the six cortices which he studied. When this is compared with the variation which Franz (1915) found in plotting the extent of the region from which he could elicit movements of leg and arm by stimulation, a certain similarity is evident.

The much needed correlated investigation of the extent of electrical excitability, and the field of Betz cell distribution in the individual animal was carried out by Langworthy (1928) on the cat's hemisphere. He divided, arbitrarily, the anterior sigmoid gyrus into three smaller areas designated by letters A, B, C; the gyrus sigmoidius posterior into three corresponding regions F, E, D; and the gyrus proreus into G, H and I. Stimulation of areas A and B with small induced currents gave well marked contractions of the musculature of the hetero-lateral foreleg. Stimulation of C produced contraction of the facial and masticatory musculature. Regions E and F caused flexion and extension of the opposite posterior extremity. No other regions of the cortex gave any response even to strong current. Smaller areas were often found within the larger, from which limited reactions were obtained. These latter varied greatly in the individual animals. Unilateral removal of the posterior sigmoid gyrus was followed by noticeable weakness of the hetero-lateral musculature, particularly of the hind-leg. Bilateral removal of this area (D, E, F) caused more marked paralysis of the posterior limbs. Ablation of the anterior sigmoid gyrus resulted in a weakness of the opposite musculature of the shoulder and forelimb. If on the other hand the gyrus proreus (area frontalis, in the cat) was removed, there was no paralysis, and but little weakness, in the hetero-lateral extremities.

Microscopical examination of the three areas in the anterior sigmoid gyrus proved them to be motor in type. The outer pyramidal lamina were wide; the granular layer, practically absent. Giant pyramids were the most conspicuous feature of the infragranular region. The same may be said for areas E and F of the posterior sigmoid gyrus. But D, which gave no response upon stimulation had no layer of large pyramidal cells. On the other hand its granular or stellate layer was wide. Area B has all the histological characteristics of the motor cortex (field 4) of Brodmann. In area A, a few granular cells are found; the supragranular lamina was broader and the infragranular pyramids smaller than in B,—characteristics of the area frontalis. This premotor cortex extends forward into the first division of the gyrus proreus. Since there was no

sharp transition between the structure of areas A and B, but each was characteristic of the area frontalis and the motor cortex respectively, we may consider that we are dealing in A with a region which in certain points resembles the small-sized Betz cell regions of the frontal lobe of Macacus. Also, apparently we find in area A, prefrontal cortex, the physiological features of B, but not its histology. If, then, A contributes no fibers to the cortico-spinal tracts, it is possible, apparently, to stimulate these tracts, not through the outer layers of the motor cortex itself, but, rather, through a contiguous region.

Holmes and May (1909) have demonstrated that the chromatolysis following cutting of the pyramidal tract in the upper cervical regions of the spinal cord is co-extensive with the cortical areas for the limbs and trunk as delimited in the brain of the lemur (Völsch, 1906; O. and C. Vogt, 1907; Mott and Halliburton, 1908). The same coincidence is found, also, in the brains of the cat, dog, monkey, chimpanzee and in two cases in man. In primates this area lies entirely in front of the fissura centralis and is co-extensive with a cytologically differentiated field (Brodmann and Campbell). On the other hand, the centers in the frontal lobes, from which movements of the eyes can be obtained, or the region whose stimulation produces mastication movements correspond to areas cyto-architecturally discrete (Vogt). The two electrically excitable regions are cyto-architecturally distinct in the marmoset also (Mott, Schuster and Halliburton, 1910). Langworthy's motor area A in which the Betz cells are large and conspicuous, contains no layer of granules, whereas in motor area B, which corresponds to that area in other brains from which face and eye movements may be elicited, the motor cells of the fifth layer (Brodmann) are smaller and a layer of granules is present.

The lateral surface of the frontal lobe in the brain of the gibbon may be divided by its histological structure into two general regions (Mott and Schuster, 1911); the first, a cortex characterized by the absence of a distinct layer of granules and the appearance of Betz cells; the second, by quite the opposite. The first may be divided again, in a manner similar to that of Nañagas for Macacus, into three regions, by the size of the pyramids of the subgranular layers. Giant pyramids correspond to the region which is easily electrically excitable (field 4 of Brodmann). Middle-sized pyramids are distributed over the lower part of the precentral gyrus, the mouth and tongue centers (field 6 of Brodmann), and together with a rather broad strip of small pyramids, make up the intermediate cortex. The area below the sulcus rectus

gives movements of the eyeballs upon stimulation. The cytological characters of these regions, taken with the results of stimulation, correspond rather well, so that Campbell's (1905) histological mapping of "motor" regions in the cortex of the orang and chimpanzee, actually underlie the same areas which Grünbaum and Sherrington (1902) found electrically excitable. The extension of the intermediate cortex and the restriction of the area frontalis granularis are peculiar to the gibbon, and distinguish it on the one hand from the orang and chimpanzee, and, on the other, from Cercopithecus (Brodmann) and the baboon.

The distribution of peripheral representation in the precentral gyrus has been plotted for the cortex of man in a complete manner by Krause (1911). A similar mapping was made by Cushing (1909) on two patients. The motor responses were accompanied, in the conscious patients, by a sensation of forced change of position similar to that felt following the stimulation of a peripheral nerve.

More recently Foerster (1926) has outlined areas on the lateral surface of the human hemisphere by studying the effects of operative lesions on epileptiform attacks. Thus when an area of the precentral gyrus, for example, is excised the corresponding region of the body does not share in the next attack. In this manner, together with the precipitation of the attack by the stimulation of a suspected area, he has in addition mapped a region for eye movements in the second frontal convolution similar to Leyton and Sherrington's for the chimpanzee and gorilla. Because his mapping of the motor cortex corresponds to those made for man by Cushing and Krause, the method seems reliable, until we see that Foerster has extended the localization of site for limb representation across the central fissure. It will presently be seen that in circumscribed injury to the postcentral gyrus no such complete representation is found.

Although we have established that there is a certain correspondence between the distribution of the giant pyramidal cell and the extent of the electrically excitable cortex, and although it is evident that there is a certain representation of body regions, matching somewhat the distribution of the cortico-spinal and cortico-bulbar tracts, nothing has yet appeared which would give us a hint of the function of this region. The result of lesion of the pyramidal system, either in the internal capsule or in the cortex, is generally paralysis, accompanied by heightened tendon reflexes, spasticity and, finally, by contracture, with such gross modification of so-called "voluntary movement" that this has been considered lost. Consequently, it is not strange to find that to the pyrami-

dal tracts has been assigned the function of transmitting to the "final common pathway" the excitation for movement initiated apparently voluntarily in the motor cortex. We wish to press some of the recent studies for a better understanding of the function of this important region. This work falls naturally into three varieties; first, study of this region by electric stimulation, not for mapping, but rather for its end result in movement, read in two isolated muscles, an agonist with its antagonist; second, restoration of function following ablation of parts of the motor cortex in primates; and third, the modification of movement and sensation following small circumscribed lesions in man.

The reaction to stimulation of cortical points outlined in any map of the motor area in monkeys and anthropoid apes, is easily altered by slight and transient changes in narcosis, blood supply or temperature. When these conditions are kept constant, however, another source of variability of cortical response, subject to experimentation, becomes evident. Graham Brown and Sherrington (1912) isolated and arranged two antagonistic muscles (the supinator longus and the humeral head of the triceps) for graphic registration. In serial stimulation (2 seconds' duration, repeated at 2 second intervals) of the cortical points which yielded either flexion or extension at the elbow, the latent period is progressively shortened, the amplitude and intensity of the muscular responses may increase, a maximal contraction may be maintained and, peculiarly enough, primary flexion may give way to primary extension. If stimulation of the flexion point is interpolated between two stimulations of the extension, the latter may be suppressed, reduced, or partially reversed; that is, the extensor contraction may be inhibited and the flexor response dominate. If, on the other hand, the extensor point is interpolated, the response of the flexor may be lessened and retarded but it is never completely suppressed, and reversal is never complete, never beyond relaxation of the extensor muscle. Further, the responses of these two points may be modified by the stimulation of an afferent nerve (nervus ulnaris). Thus stimulation of the flexor point after stimulation of the nervus ulnaris relaxes the reflex flexion, whereas the extensor point is reversed. If, however, the latter is stimulated very strongly it may break through and suppress the afferent nerve. If after a muscular response the motor cortex is reached by stimulating the postcentral gyrus, this movement may return after its cessation, or the epileptoid after discharge, following on stimulation of a motor area, may be modified. These results appear to demonstrate that the activity of the flexion point is always slightly more dominant than that of the

extension. Certainly when these two are aroused concurrently, the flexor point may break through the extensor and establish flexion. The extensor may do the same, but algebraic summation of the two movements is more common. These authors report that on several occasions cessation of a cortical stimulus causing inhibition of a muscle, was followed by contraction of that muscle, a phenomenon similar to "rebound" in spinal preparations.

This type of investigation has been elaborated in some twenty-five papers by Graham Brown. For further elucidation of the activity of the motor cortex, let us select one of its characteristics as studied,—facilitation. This operates under various guises, for example,—the time interval for liminal strengths of stimulation is approximately ten seconds; a second response is greater if it falls within this interval although the strength of the second stimulus remains the same. Facilitation varies with the strength and duration of the previous stimulation. Thus, if a series of activating stimuli of constant strength are altered by increasing their durations, the subsequent test series may show progressive diminution. With weak stimuli the responses may be progressively augmented and with strong stimuli, progressively diminished. Again, a previously evaluated subliminal stimulus, when applied to a flexion point in the cortex following excitation of a more excitable flexion point, may become supraliminal in value,—secondary facilitation. Since this phenomenon may be abolished by a transverse cut with a knife through the cortical substance between the two points, facilitation acts, apparently, in the cortical material itself. Since secondary facilitation is located within the cortex, Graham Brown believes that there is good reason to think that the primary process may also be partially located there. Moreover, he found the latter phenomenon also characteristic for stimulation of the nerve fibers of the corticospinal tracts immediately below the cortex, in the internal capsule and in the basis pedunculi. Further in the stimulation of the pyramidal tract a certain grading of reaction in response to the grading of the stimulus was described. Nevertheless, the condition of progressive augmentation of responses to repeated stimulation of the subcortical system is not only difficult to demonstrate but is also more irregular than that of the cortex itself. Apparently there is a finer process of primary facilitation found in the motor cortex. Now, if a previously tested flexion point is removed by ablation, the strength of stimulus necessary to evoke motor responses is much greater than that which had evoked responses

from the points contained in the area removed. The cortex may lower the threshold for stimuli given it.

Leyton and Sherrington (1917) found facilitation more effective in the anthropoid cortex than in that of lower monkeys. By its use the excitable cortex may be made to extend further forward, or a region, arm or leg, to exceed its usual limits. It is not impossible that in the overlap of arm and leg areas plotted by Franz (1915) for Macacus rhesus facilitation was at work. By "deviation of response," is meant the influence on the response from one cortical point of previous activity to another somewhat similar point. Thus, for example, after a complex movement (342) had completely subsided, stimulation of a motor point commonly yielding plantar flexion of the ankle, flexion of all toes except the hallux and adduction of the hallux (movement 319) resulted instead in flexion at the hip, dorsal flexion of ankle and knee and flexion of all toes except the hallux.

From such studies as these, it becomes apparent that lability of function, facilitation and deviation of response is even more characteristic than localization of activity within the motor cortex. Combination of discrete movements into a coördinated whole is more evident in the anthropoid cortex than in that of monkeys or of such laboratory animals as the rabbit, dog and cat. In the anthropoid cortex, flexion of one joint may be followed by extension of another and flexion, again, of a third. This combination of sequences is just that which would naturally appear in any particular purposive motor response. In the anthropoid cortex diagonal movements such as are often elicited in electric stimulation of the dog's motor cortex were not seen. And in the dog, the results of cortical stimulation are not contraction of separate muscles but contraction of definite muscle groups, followed by others in a manner which might be interpreted as movement sequences, characteristic of walking. In the cat, however, movements of the forelimb are more easily separated from a following contraction of hindleg musculature,—more evidence for the greater independence of the foreleg. Further, Leyton and Sherrington thought that many of the observed facial movements suggest mimetic acts; others, those concerned in feeding. The cortex can, apparently, break up the simple flexion or extension of lower centers into new combinations, each following the other in a well timed sequence,—a synthesis of movement made up of grosser entities. These investigators found that both complicated, successive movements and partial discrete ones are equally characteristic of the results of cortical stimulation in animals. These partial

movements, highly coördinated with others to express apparent "intention," yet separately elicitable, become more evident, the more highly differentiated the cortex. May not this instability, lability, be the basis of educatibility of the motor cortex?

What happens, now, when the motor cortex is removed? Graham Brown and Sherrington (1913) removed the arm area from the left motor cortex of a chimpanzee. Five months later there was no obvious difference in the movements of the two arms, when the area for the left arm was ablated. Almost two months later, the postcentral convolution on the right was destroyed opposite the region already removed. None of the movements of the left arm were lost by the last operation, although there was considerable weakness. Two months afterwards the animal was able to transfer a banana from one hand to the other without watching either hand. These investigators did not think that the recovery was due to regeneration of the area destroyed, nor to the taking over the function for movement either by the corresponding area of the opposite motor cortex or by the postcentral cortex.

This type of ablation was extended and restudied by Leyton and Sherrington (1917). In that year they reported an excision of the arm area in the left hemisphere of the chimpanzee (Troglodytes niger). Six weeks later the movements of the right shoulder and elbow seemed perfect. The wrist was moved well, although often held in a drooping pose. The movements of the fingers showed the greatest defect. The index finger was never moved separately. The thumb of the paretic side combined with the fingers in a general clasp, but never had the power of the normal group; not a marked change—but one which corresponds closely to the defect found in man subsequent to small lesions of the motor cortex. This region was re-exposed; no stimulus in or about it could elicit movements of the right arm. The cortex surrounding the old lesion was removed. There was no change. This experiment was repeated on another animal. After the animal had apparently recovered use of arm and hand except for a certain clumsiness of the fingers, the wound was reopened and made greater. Faradization of the parts left gave no response and the activity of the animal was as before. At a third operation, the opposite (right) hemisphere was exposed. Its stimulation gave no movement of the right arm; only of the left. This arm area was removed. The symptoms of paresis and clumsiness were localized in the left arm. The second operation was repeated on the left and the results were approximately the same. At a fifth operation the postcentral gyrus opposite the motor area was

stimulated; it gave no response. Certainly there is no evidence here that the motor cortex of one side assumes the function of the other. Nor was it possible by this type of experimentation to localize any point elsewhere in the cortex which might be thought to be compensating the loss.

These results of Leyton and Sherrington elucidate those of Franz and Lashley upon removal of the motor cortex of animals which had been taught a certain sequence of movements directed toward securing food. The white rat can learn to "run a maze" after the removal of what Franz and Lashley (1917) call the frontal pole, which, apparently, includes all the electrically excitable cortical areas. The animal, however, does not retain the previously learned habit even when by operation only the regions which yield movements of head and neck were excised, although such an operation was not accompanied by more than the merest transient paralysis (18 hrs.). In a further study, Lashley (1920) reported that destruction of the motor region was followed by an apparent increase in general activity of the animal, although loss of a similar amount of nervous tissue elsewhere in the cortex gave no effect, —an increased activity which reminds one of the restlessness of Goltz's decorticated dog. These rats, likewise, were capable of learning at the normal rate, kinaesthetic or visuo-motor habits, after destruction of any given part of the cortex. Only habits which depend upon brightness-discrimination were lost by injury to the area striata of the occipital pole. Further, these animals are able to acquire somaesthetic motor habits not only after destruction of the motor cortex (electrically excitable areas) but also after destruction of the caudate nucleus. Although this combined destruction gave motor disturbances resembling the hemiplegia of monkeys, nevertheless simple somaesthetic motor and visuo-motor habits were retained. Difficulty was observed primarily in the assumption of new postures. Lashley concludes, therefore, that the motor cortex of the rat is not a region which carries out motor adjustments evident in the formation of habits, but rather that it is postural and facilitating in function.

Lashley (1924) reached practically the same opinion for the motor cortex in Macacus rhesus; for, when animals had recovered from the paralysis following bilateral destruction of this, they showed retention of habits of manipulation and visual discrimination which they had previously learned. Subsequent destruction of the corpus striatum gave no return of the cerebral paralysis. However, the latter lesion, if outlined correctly, implicated only the head of the nucleus caudatus

and the anterior part of the putamen. The globus pallidus must have been very nearly intact. Therefore, if Wilson (1914) is correct in his view that the corpus striatum is, in Macacus, entirely independent of the cortex, irrespective of the condition of the globus pallidus, the remaining cortex would not be able to discharge through it.

What implications these results have for man is undetermined at the present. Although Franz (1917) can restore a hemiplegic monkey by massage, electrical stimulation and forced use of the paralyzed limb, not in six months, if it be left to its own devices, but in three weeks, this rapid recovery is "practically complete." In just that difference between complete and "practically" complete lies the material for the final analysis of the function of the motor cortex in these animals. The reviewer does not wish to minimize the hope that such a finding offers to those interested in a similar recovery in man, but, even in man, there is a marked difference between normal and recovered muscle groups in their approach to the limit of use.

From the data furnished by Franz and by Lashley, there are, apparently, great possibilities for reëducation of motor control after severe losses of cortical tissue. These observations make one hesitate in assuming that the activity manifested by this region is on what might be called the level of awareness. This corresponds well with Sherrington's observation of the apparent surprise shown by the chimpanzee, when the paretic limb failed to execute its accustomed movements. The failure was in execution alone. Again, Cushing's conscious patients said that there was no awareness of the stimulation of the motor cortex other than that which accompanies any forced movement of a part. It seems only logical to believe that it is the proprioceptive excitation resulting from movement, which lends us awareness of it. And if so, it is not surprising to find Sherrington's chimpanzees unaware of a loss of cortical function.

The motor cortex of man. The peculiar distribution of paralysis in the periphery following severe injury to the motor cortex or hemorrhage into the internal capsule, was first described by Wernicke (1889), and since has been the subject of many inquiries by savants of clinical neurology (Mann, 1895; Van Gehuchten, 1897; Rothmann, 1904; von Monakow, 1905; Foerster, O., 1909; Lewandowsky, 1910; Gierlich, 1913). The disturbance is greater in the distal segments, in the foot or hand, than in the elbow or knee, the hip or shoulder. Again there is a difference in particular distribution among the muscle groups of the limbs themselves. In the leg it is most severe in the flexors; in the arm,

in the extensors. It is difficult to open the hand. The lower limb is rotated outwards, the upper one inwards. Dejerine (1909) found that the muscles concerned in respiration were not paralyzed; that on the injured side voluntary inspiration and expiration were possible, but the excursion was never quite equal to the normal.

The facial musculature is often affected, commonly only that about the mouth, the orbicularis oculi and the muscles of the forehead being often spared. The glossal musculature is weakened, so that the tongue deviates to the paralyzed side. The uvula takes the opposite position when its musculature is injured. The muscles of the jaw are lessened in their power of movement forwards and sideways but not paralyzed. The intrinsic muscles of the larynx are not markedly affected in a one-sided lesion, although a difference can be demonstrated.

As far as the reviewer could determine there is no adequate explanation for this peculiar distribution, either of weakness in one set of muscles or of what appears to be a corresponding increase of tone in the opposing group. Walshe (1923) has attempted to explain the habitual postures of human hemiplegics as a phenomenon in man similar to decerebrate rigidity in animals. Graham Brown reports that in a decerebrate preparation of a monkey, the increase in tone is found in the extensors of the hindlimbs and the flexors of the fore. Gierlich has suggested that the muscle groups most affected by hemiplegia in man are identical with those which had an extraordinary meaning in the movement combinations necessary for the first phase of brachiation in the higher apes. This flight occasioned, so he thinks, the recent introduction of the innervation of such a muscle group into the cortex, because of the higher intellectual performance required in its innervation. So he would explain the dominance of the flexor point over the extensor in the arm area of apes.

And yet in spite of the great similarities of the motor cortex in ape and in man the importance of its intactness for the maintenance of normal posture in the latter is apparently greater. In his interesting comparative study of posture in hemiplegic man and in normal apes, Brain (1927) pictures a change in position of the arm when the quadruped attitude is assumed—the quadrupedal extensor reflex. If the hemiplegic man flexes his body at the hips, the affected hand may come to rest upon a chair. The arm is flexed at the shoulder, more strongly adducted and internally rotated and extended at the elbow. The pronation of the forearm is increased, the wrist and fingers flexed. Now if the weight of the body is partially assumed by the upper limb upon the

chair, the wrist and first phalanges are extended, the distal joints of the fingers are flexed and the dorsum of the two terminal phalanges are in contact with the surface. In this position the extensor tonus of the affected limb is diminished by ventro-flexion of the head on the neck and increased by torso-flexion. In other words, when the hemiplegic arm partially supports the weight of the body it takes a position identical with that of the free limb of a chimpanzee, at rest. On the other hand, shifting from erect standing to erect sitting to erect squatting (postures peculiar to man) is characterized by a progressive increase in the flexor tonus of the affected forelimb. And although in decerebrate preparations of both monkeys and man (Wilson, 1920) the tonus of the flexors is greater, the quadrupedal extensor reflex appears in the latter when the anthropoid position is assumed only when the projection tracts from the motor cortex are interrupted.

The hypothesis of Gierlich may work also in the opposite direction, for though the chimpanzee has cortical representation for facial musculature, its removal gives no paralysis. Thus after Sherrington had removed all the parts of the cerebral cortex from which he could get movements of vocal or facial musculature in a young chimpanzee (Troglodytes niger), there was no facial or other paralysis and certainly no impairment in the variety or amplitude of his voice sounds; in fact he was "more noisy than ever." The cortical representation of the facial musculature is not new; it can be shown by electric stimulation, even in marsupials (Gray and Turner, 1924). But facial paresis following injury to the pyramidal tracts is, apparently, peculiar to man.

Now, although Franz and his co-workers (1915) have demonstrated that training can restore to a marked degree the hemiplegic man, nevertheless there is never quite the return toward normal which is seen in monkeys or apes. But, again, the lesions in apes and man are hardly comparable. Those of the latter are larger, implicating greater areas of the cortex or internal capsule, and occur commonly in later life, whereas experimentation is usually performed on young animals. But Horsely (1909) has provided, perhaps, one human "experiment." Horsely removed from the right hemisphere of a boy all the cortex from which he could elicit by electrical stimulation any arm movement. The patient was examined three years later by Head. At that time, the bulk of muscles of the left forearm and hand was less than of the right and their tone was increased. The limb was rigid but no organic contractures were present. So-called "voluntary" power was diminished in the left arm, particularly in the fingers, but movements at the shoulder and

elbow were of fair strength and good range. The arm jerks were exaggerated on the left. The sense of position of the limb was grossly defective, this loss affecting all joints, but especially the fingers and elbow. The compass test was defective on the hand, and appreciation of weight was gravely disturbed. Tactile recognition on the left was slower and less constant than on the right, and the sensation often outlasted the stimulus. The appreciation of roughness and vibration, tickling and scraping, pain and thermal sensibility was the same for both arms.

This case introduces a new element into the peripheral losses following cortical injuries—a sensory moiety—that, particularly, of sense of position. There has never been any attempt made to examine apes for such loss. Attention has been focused on motor phenomena. It is not impossible that the peculiar gravity of injury to this cortex in man results not entirely from motor defect, but rather from disturbance of movement combined with its subsequent appreciation. Head says that this boy played tennis; certainly as severe a test for the return of movement sequence as any put to monkeys or apes. This case is what might be called a "practically complete" recovery, but the discrepancy between the recovery and the normal still is great. It is just that difference which is so important for our understanding of the function of this area.

In Head's (1920) study of small circumscribed superficial injuries, particularly in the parietal lobe, a few were lesions of the precentral gyrus. Out of the seven injuries to the precentral gyrus only two involved that gyrus alone. The remaining five also implicated the postcentral convolution. By subtracting, he gained an idea of the loss which was characteristic of each. Bénisty (1918) also reported lesions of this region, but it happened that these were large when compared to those of Head, and none was a completely isolated lesion of the ascending frontal convolution.

Lesions which involve the precentral convolution, or which cut across the postcentral and precentral gyri, have one gross symptom in common (Head, 1920),—loss of spatial recognition. Head used three methods of testing such loss; first, the appreciation of a measured passive movement; second, the compass test; and last, "spot finding." The disturbance of sensibility as revealed by these three tests is graduated. "Spot finding" presented the easiest problem to the patient, for it was least affected; the compass test somewhat more, and passive movement, most severely. If the injury was slight, only the last might be defective.

Head considers that these clinical tests represent, in a certain way the appreciation of dimension and that the loss of appreciation of passive movement is a three-dimensional loss. Localization of certain parts of the body characterized these lesions in the cortex. In injury to the paracentral lobule, the difficulties were found in the foot, while for the upper pre- and postcentral gyri, they were more or less confined to the shoulder, elbow and wrist. Head's case no. 21 is probably the clearest demonstration, for here the injury was fairly small and confined to the middle of the precentral gyrus. The whole hand and elbow showed a loss of passive movement and a want of appreciation of weight, but tactile sensibility was unaffected. If, on the other hand, the post-central gyrus was involved, special tactile sensibility was profoundly diminished in the hand. The power of recognizing differences in weight and form was most severely disturbed but there was other sensory loss also. Such were not seen in two of his patients (no. 13, and no. 21) whose injuries were mainly precentral.

Bénisty (1918) found somewhat similar sensory losses in instances were the lesion was confined to the pre- and postcentral gyri. For example, in her first case, which was a large injury in the lower part of the upper half of these two convolutions, what she called stereognosis was completely abolished; recognition of the attitude of the fourth and fifth finger was wanting; vibratory sensation was attenuated and the circles of Weber were enlarged and localization defective. There was, in addition, a diminution in tactile sensibility, in pain and in heat over the last three fingers. In other lesions of comparatively the same extent and location, the same variety of sensory loss was found, with the exception that tactile sensibility was intact. Since she did not attempt to analyze her findings after the manner of Head, it is significant that the loss of sense of attitude and stereognosis, as well as the impairment of two point localization were, apparently, of a similar order of magnitude in the two studies.

There must have been a difference not only in the extent of the lesions studied by these two investigators, but also in their depth. In his more superficial lesions, Head found no paralysis. The fingers could be held in alignment unless the eye were closed; they were neither spastic nor hypertonic. Neither was tone increased in the arm, although the elbow and wrist jerks were exaggerated. Such a patient (no. 8) presented the picture of "practically recovered." Whereas before he had been a good tennis player, two and a half years after injury he was "terribly bad." Bénisty concluded that the greater the sensory trouble the less

the reflexes were modified and that exaggeration never appeared if the injury avoided the ascending frontal convolution. Exaggeration occurs then with lesion of the precentral gyrus, and more frequently where more white matter is involved,—that is, with deeper lesions.

From this meagre review, it is apparent that the more superficial injuries of the motor cortex in man resemble in certain respects, particularly in recovery, those produced experimentally in apes. But the common lesions whose extent cannot be gauged,—emboli or cerebral hemorrhage, or injury to the cortici-fugal fibers as they pass through the internal capsule,—are the injuries which have given the accepted clinical picture,—paralysis, contracture, augmentation of idio-muscular contraction and associated movements. Seemingly the motor cortex presides over fine individual movements, especially of the extremities. It regulates the distribution of tone in opposing muscle groups. It exerts apparently a certain restraint on reflexes and associated movements. It integrates, or perhaps interprets, certain incoming impulses which are necessary for the coördination of movements and movement sequence. Moreover, it facilitates, augments and aids in gauging the amount of contraction of individual muscles or groups. And facilitation may be used in the special sense of Sherrington or Graham Brown or with its ordinary connotation, that the motor cortex makes the initiation of change of position easy. Movements on a lower level in man apparently need a greater affective quality for their initiation. Certainly in man, the ascending frontal convolution does more than regulate posture, if posture is taken in the limited use, as the standing reflex. The motor cortex may not be the site of origin of voluntary movement nor the gate through which learned movements pass, but certainly it assures to man that his muscular adjustments take place in the way to which he is accustomed and without undue effort or strain. Consider Head's patient no. 8. He could still play tennis, but not as well; he could still write, but the form of his letters did not have the perfection which was once theirs.

THE PARIETAL LOBE AND THE SOMAESTHETIC CORTEX. The parietal lobe of man is divided by Economo and Koskinas into four great regions, —regio postcentralis, regio parietalis superior, inferior and basalis. The regio postcentralis is the postcentral gyrus of other authors; the regio parietalis superior, the superior parietal lobule; the regio inferior contains both the supramarginal and angular gyri; and the basalis is a strip of tissue (field 37 of Brodmann) which lies between the posterior limit of the temporal gyri and field 19 of the occipital lobe. Generally,

the anterior half of the latter area is considered as belonging to the temporal lobe and the posterior half to the occipital pole.

Brodmann distinguishes four cytologically distinct areas in the postcentral convolution (fields 1, 2, 3, 5), two more in the superior parietal lobule (fields 7a and 7b), one for the supra-marginal gyrus (field 40), one for the angular (field 39) and one for the regio parietalis basalis (field 37). The limits of these specialized areas correspond rather well with those outlined by Economo and Koskinas.

The cortex of the major portion of the gyrus postcentralis (field 3) is thin compared with its neighbor across the central fissure, and is characterized by a thick receptive layer (IV) and by large pyramidal cells in the lower reaches of the third layer. Moreover, the deep pyramids of layer five are smallish, comparing strikingly with the large ganglion cells of the adjacent area praeparietalis (field 5). The superior parietal lobule (field 7), on the other hand, is a cortex of medium thickness, with large pyramidal cells in layers III and V and an especially deep receptive lamina (IV).

The cortex of the gyrus supramarginalis is rather deep. The cells of its well developed lamina are small and layers II and IV are marked by prominent transverse bands of fibers. This cortex belongs, therefore, to the granular parietal type of Economo and Koskinas. Its caudal neighbor, the gyrus angularis, however, resembles, in its narrow third layer, the area parietalis superior. Flechsig found this to be an area of late myelinization and hence thought it an association center.

The area parietalis basalis (field 37) is cyto-architechtonically an occipito-temporal transition cortex. Of medium depth and rich in small cells, it possesses broad outer and inner granular layers. This area, together with fields 39 and 40, was considered by Campbell as belonging to the temporal lobe.

According to Brodmann's analysis of the homology of the parietal lobe, areas 1 to 3 of the postcentral gyrus are present, and 5 and 7 as well, whether the brain be that of Hapale, Lepus caniculus or Cercopithecus, but cortex of the type of the gyri supramarginalis and angularis is not found. Comparing the relative amounts of brain surface given to areas 5 and 7, Kappers finds that in carnivores area 7 is as large as area 5; in the lower apes, twice as large; and in man, more than four times.

The sensory cortex of carnivores (the gyrus postcrucialis) is related by fiber systems to the lateral and ventral nuclei of the thalamus and also to the motor cortex (the gyrus precrucialis). von Monakow (1895) finds that Brodmann's area 7 of the gyri suprasylvius and lateralis of

the dog's cortex receives thalamo-cortical fibers from the anterior and lateral nuclei of the thalamus and from the pulvinar. In the macaque, Sachs (1909) described thalamo-cortical systems from the lateral nucleus, going in part to the post-central convolution but the major portion to the precentral gyrus. Peculiarly, although Sachs produced electrolytic lesions in all the larger nuclei of the thalamus in Macacus rhesus, he reported no cortici-petal fibers for area 7 of the parietal lobe.

The cortico-thalamic relations of the parietal lobe in man appear vague because lesions are not discrete. Dejerine (1901) found some retrograde degeneration in the lateral nucleus (optique couche) following lesions of the Rolandic zone, a finding similar to those for the cat, the dog and the macaque. In addition, however, he noted slight indications that the superior parietal lobe is the origin of a cortici-fugal system to the lateral nucleus. Dejerine emphasized the connection of the pulvinar with the visual cortex, yet, in passing, he mentioned that some of its fibers also pass directly to the gyrus supramarginalis. These latter Kappers associated with the increasing importance of stereognosis in primates where binocular vision and a free fore limb allow for the close scrutiny of an object. Exact data on the subcortical fiber relationships of the superior parietal lobule and the gyrus angularis are meagre.

The "somaesthetic" cortex does not correspond exactly to the limits of the parietal lobe as given by Economo and Koskinas, for it does not include the area parietalis basalis. Moreover, the precentral convolution cannot be considered as a part of the parietal lobe, yet certain physiological results of injury to the latter gyrus force us to discuss the possibility of it belonging to the "somaesthetic" area. The somaesthetic cortex comprises, therefore, the postcentral gyrus, the superior parietal lobule, and perhaps the precentral convolution, the supramarginal and angular gyri.

The analysis of that region of the cortex which receives the general sensibility of the body yields such meagre results to the methods of animal experimentation that little work has been done on it since the decades of Munk's activity. The more fruitful fields of motor activity have been too attractive. Dusser de Barenne's (1916) recent attempt to map the representation of corporeal sensibility by strychnine sensitization of the surface of the cat's cortex stands out in almost complete isolation. He is thoroughly aware of the criticism which such an experimental procedure may deserve; nevertheless his results are clear cut and therefore worthy of consideration. He found the head, neck

and limbs well localized. The regions of maximum sensitization for the limbs resembled roughly the similar areas outlined by Munk's ablation experiments in the dog. There was some overlap onto the fields so nicely determined by Langworthy as motor and premotor. And certainly it is not surprising that the upper layers of the cat's motor cortex should control some of the finer aspects of proprioceptive and even of cutaneous sensibility, for Sachs has found that these regions receive fibers from the lateral nucleus of the thalamus. Generally speaking, the strychnine sensitization was evidenced more clearly in the more distal divisions of the limbs. If Dusser de Barenne's interpretation be correct, those portions either have greater representation in the cortex or possess, perhaps because of such representation, a lower threshold of stimulus. Cutaneous sensibility is bilaterally represented: although the contralateral forelimb was more grossly affected, the ipsilateral also suffered. And in those regions which were related to both fore- and hindlimbs, the forelimb was affected ipsilaterally and the hindlimb contralaterally. Proprioceptive representation is, however, completely hetero-lateral.

In Sherrington's laboratory, Dusser de Barenne (1924) later applied these experimental procedures to the cortex of the macaque (M. rhesus and M. nemestrinus). In these he found that hyperalgesia and hyperaesthesia could be produced by strychninization of the pre- and postcentral gyri and of the regio parietalis inferior. Furthermore, no changes of any description were observed following a like treatment of the frontal lobe anterior to the sulcus arcuatus or of the gyrus temporalis superior. By this technique Dusser de Barenne distinguished within the "sensory" cortex a narrow leg area lying across the top of the central fissure, a broad arm area in the center, and a large region for the face at the foot of the Rolandic zone. And if when strychninizing either the arm or the leg areas a little of the drug passed the boundary between them, hypersensitivity was present on the trunk also.

From a unilateral sensitization of the cortex, a bilateral cutaneous hyperalgesia and hyperaesthesia resulted, but more extreme in degree hetero-laterally. This bilateral hypersensitivity did not disappear when the non-strychninized corresponding area was removed. After such an ablation, however, the monkey no longer touched the spot stimulated, whether it was pricked, pinched or touched with a hot wire. Deep sensibility was sometimes disturbed hetero-laterally, sometimes bilaterally, but always to a more exaggerated degree on the opposite side.

Although sensory disturbances were elicited from strychninization of the cortex anterior to the central fissure and even anteriorly beyond the

limiting zone of the motor cortex, yet the procedure altered in no way the response of this cortex to the electric current. Furthermore, there were no marked muscular reactions following the application of the drug to the motor cortex, although within a short interval after its application small twitchings were observed in the opposite limb.

As in man, then, the motor cortex of the macaque as well as the postcentral cortex is apparently sensory. In the monkey there seems to be no distinction between the localization of deep and cutaneous sensibility in the precentral convolution. And dissimilar to the observations upon the postcentral cortex in man, as will soon be apparent, the region outlined by Dusser de Barenne for the representation of the face, occupies a larger area than does that for the hand.

In order to understand any analysis of disturbances in somaesthetic sensibility dependent upon cortical injury, it is necessary to consider, first, the author's hypothesis for the subdivisions of sensation, and second, his methods of testing loss of sensibility.

After cutting a cutaneous nerve sensibility to prick, temperature, touch and light pressure disappear simultaneously, while that to deep pressure, however slight, and to vibration remain undisturbed together with sense of position and of passive movement. The latter group are distributed through the muscle nerves. Among the former, the first to return is the sensibility to prick. In certain areas of cutaneous distribution this return appears first at the periphery, within 6 or 7 weeks and throughout the whole anesthetic region 5 or 6 weeks later. The recovery of sensation to prick is, however, not exactly that experienced from a similar stimulus on a corresponding normal region. The amount of stimulus (prick) necessary to evoke sensation is at first greater over the affected part; the sensation radiates, is poorly localized, or referred to a distant part and is accompanied by an affective quality without awareness of the type of the stimulating instrument. Appreciation of extremes of temperature returns next,—first of ice cold, and later, of heat above 50°C. And although these temperatures are correctly interpreted as cold and hot, nevertheless they share with prick in poor localization, marked irradiation and over effect. Light touch, intermediate ranges of temperature, light pressure reappear later; and the ability to discriminate the simultaneous stimulation of two points is so tardy that it may not have returned after sixty years.

Such dissociation in the return of cutaneous sensibility Head interpreted as evidence for a double system,—the former, a cruder type, he called protopathic; the latter, with its finer localization and discrimina-

tion, epicritic. Head believes that the first system is older phylogenetically and serves to protect the individual from noxious stimuli; the second is the newer and provides for examination of the stimulus so that its relative strength, position and size can be estimated. Head's dual concept of cutaneous sensibility, first developed for the peripheral nerves, was later applied, in conjunction with Holmes (1911), to the examination of lesions in the "optic" thalamus and the "somaesthetic" cortex.

This concept of the duality of cutaneous sensibility is severely criticized in the work of Cobb (1919), of Pollock (1920), and of Boeke and Heringa (1924). Cobb considers that if prick is properly graded, the area of analgesia and touch anesthesia are the same; thus only if the stimulus for prick is raised (from 15 to 30 grams) does the analgesia region shrink. He believes that dissociation is conditioned solely by the strength of the stimulus. And yet the prick used by Pollock to outline his areas of overlap, which disappeared after the neighboring nerve was cut, was the same value as that criticized by Cobb (30 grams). Returned sensibility in Pollock's cases was therefore not the result of regeneration.

This difficulty of evaluating their method of examining pain was not overlooked by Head and Rivers (vol. 1, p. 259, 1920). The algesimeter used by them for discovering the return of pain over the affected area, read in gram equivalents between 6 and 8, while in the analogous region of the normal hand it was 5 grams. That is, the area was hypoalgesic, the threshold for pain was raised, the stimulus more unpleasant, or more painful, and remained until the return of accurate localization,—a situation which was interpreted by Trotter and Davies as a progression from anesthesia through hypoesthesia to normal. The peculiar accentuated reactions were ascribed to irritation.

Following a peripheral nerve injury (N. ulnaris at wrist) after the characteristics of Head's protopathic sensibility had been established Boeke examined histologically a small piece of skin removed from the affected area in Heringa's hand. Everywhere nerve fibers were in the same stage of regeneration,—a finding not favorable for Head's theory. In their opinion protopathic sensibility is the result of stimulation of sensory end organs in the process of regeneration; and epicritic, that of the same end organs regenerated.

Nevertheless neither irritation nor the process of regeneration can explain the peculiar areas of skin in which protopathic sensibility remains stationary for five years (Head) or for twenty years (Stopford);

nor the dissociations of sensation described after dorsal root section in man. Further there remains unexplained by any other theory than that of Head, the protopathic sensibility of the glans penis and the extremes of temperature which are felt by the mucosa of the esophagus and stomach.

And now although this concept of duality has not received general acceptance it is interesting to note that many recent students of sensory disturbances have been forced by their material to create a similar one of their own. The methods of Head and Holmes, for example, are constantly employed in Holland in the examination of sensory difficulties of cortical origin (Brouwer, 1927). Stopford's (1922–1927) studies of degeneration in peripheral nerves have led him to extend this classification of Head's to sensation carried in the muscle nerves. He places the pain of deep pressure, undisturbed by the cutting of cutaneous nerves, with the protopathic division, and the recognition of position and passive movement with the epicritic; but Stopford does not say where he classes the sense of vibration. Parsons (1927) has been led to the conclusion that "Head's distinction of protopathic and epicritic systems is fundamentally correct in spite of grave difficulties and inconsistencies in detail." Parsons believes that many observations "point to a dual mechanism at work in almost every domain of sensation with the exception of pain." Thus his divisions are "a crude dyscritic sensibility" and "a highly differentiated epicritic sensibility." In his new monograph on pain sensibility Foerster (1927) says that the capacity for regeneration of nerve fibers mediating that type of sensibility is greater than that of all other fibers and that they show a greater resistance to noxious agents than do those fibers which carry touch or temperature sensibility. He thinks that he also has evidence for two systems,—an affective for the appreciation of pain (like Stopford, deep and superficial); and perceptonic-epicritic,—for touch, pressure, warmth, cold, especially concerned with discrimination and with spatial relations, and unconcerned with the affective quality of a stimulus.

The inability of lesions in the spinal cord to demonstrate the exact dual mechanism seen in the peripheral nerves is thought to be due to their regrouping. At the recent Neurological Congress in London Petrén (1927) referred to his investigations, published some twenty-five years ago, in which he distinguished two routes of conduction of tactile sensibility in the cord,—one which travels in the opposite ventral funiculus in the region of the pain and temperature tracts and the other in the dorsal funiculus of the same side. He suggested that the latter

may conduct discriminative types of sensibility. Certainly, when the dorsal columns are injured it is the two-point test variety of tactile sensibility which suffers (Dejerine, 1914). And even in the cervical cord tactile discrimination is the only one of the "epicritic" systems to remain uncrossed.

Head's studies of injuries to peripheral nerves have demonstrated the possibility of a loss of deep pressure simultaneous with an intact sense of position and passive movement for a definite region. It is apparent that these two types of deep sensibility are carried to certain parts at least by different peripheral systems. In the cervical cord they are separated in a manner similar to that of the tactile systems. None from deep sensibility, only those which carry the appreciation of position and passive movement are uncrossed. The ascending systems, between the two dorsal horns, in man are phylogenetically new (Brouwer, 1927), although proprioceptive sensibility is not. Apparently it is certain aspects of the sense which are new—those aspects perhaps which travel in the dorsal funiculus via the medial lemniscus to the thalamus and the somaesthetic cortex. The older fiber tracts for this system, the spino-cerebellar pathways, correspond in age to those of cutaneous sensibility, the spino-tectal tracts. Both suffer great modifications by acquiring direct relations with the thalamus and in the case of proprioceptive sensibility apparently a new tract has arisen.

Such classifications of pain as those which respond to prick (cutaneous) and to deep pressure (traveling with the muscle nerves) do not consider the various forms of dysaesthesiae, in which pain is such a prominent clinical entity. From studies of such conditions Wilson (1927) believes that besides the ordinary afferent peripheral path for pain (peripheral nerves, posterior spinal roots, cord) there are two others: 1, vessel plexuses, peripheral nerves, spinal roots; and 2, vessel plexuses, aorta, sympathetic paravertebral chain, white rami, posterior roots. It is not impossible that the lack of recognition of the last two, particularly the second, may be one of the confusing elements in the analysis of the subdivisions of sensibility.

The understanding of cutaneous sensibility is not furthered by denial of the hypothesis of Head. Two anatomically distinct systems may not exist; they have not as yet been demonstrated. It is possible of course that the same fiber mediates the two, leaving discrimination and localization as a function of cortical interpretation. And if so, what of the "all or none" law, which physiologists have been at so much pains to establish for the peripheral sensory fiber? Certainly, ambigu-

ity is present; and until peripheral conduction has yielded to a clean cut analysis, there is little hope in understanding completely the function of the somaesthetic cortex. Nevertheless, it is interesting to note that the use of Head's classification of cutaneous sensibility as protopathic and epicritic lends an analysis to studies of thalamic and cortical injuries, which is never achieved in those which are simple reports of examinations of damage to sensibility. And that is the function of an hypothesis.

In making a comparison of the recent studies by Head and by Bénisty (1918) of lesions in the parietal lobe, it is first necessary to compare their methods of testing sensation. Bénisty used the methods of Dejerine; Head, not only those already elaborated by von Frey and Henri but others of his own devising. Behind Head's work was the intent to analyse, for various levels of interruption, the loss suffered by the components of sensation. Also, he wished, if possible, to establish for each level a threshold of response, and to give to the cortex an opportunity to demonstrate any peculiarity of integration which it might possess. The threshold for proprioceptive sensibility was the measured angle of displacement at which the individual became aware of passive movement. Temperature sensation was studied, not by the simple recognition of hot and cold, but rather by the discrimination between variations of degrees centigrade in either direction. The threshold for appreciation of roughness was determined by Graham Brown's aesthesiometer; that for superficial pain by a spring algesimeter, and for pressure-pain by an algometer; for pressure-touch, a pressure-aesthesiometer was used and cotton wool or a camel's hair brush for light touch. After the thresholds of these various sensations were established, their integration was studied,—first, by localization of the point stimulated; and second, by such appreciation as of weight, size, shape in two or three dimensions and texture.

Bénisty's methods were incomparably grosser. Tactile sensibility was judged by localization, the circles of Weber and a change in the time of response. Pressure was determined by an aesthesiometer of the Salenburg type. From the context the writer would consider that her "stereognosis" was tactile perception in space and resembled Head's use of shape, form and texture.

The German investigators have also been influenced by Henri and von Frey so that their methods of study of somaesthetic loss following cortical injury are similar to those of Head. For prick-pain and temperature sensibility no particular apparatus was described. For pres-

sure Goldstein and Gelb (1920) used Goldscheider's baraesthesiometer. Touch was explored with an Ebbinghaus apparatus and localization requested. The two points of the compass test were given simultaneously and successively. The knowledge of size and form were estimated as follows: evaluation of the length and thickness of small rods; differentiation between an angle and a curve; discrimination between a triangle, an oval and a square; again between a pyramid, a four-sided prism, a sphere and a cube; and recognition of such objects as a key or a knife. Passive movements made on the normal side were repeated on the affected side (eyes open and closed), together with a statement of direction and amount of the latter. Movements common in ordinary life were also utilized. In such a manner, what the patient can and cannot do, is clearly and objectively outlined.

To facilitate our understanding of the part the somaesthetic cortex plays in the analysis of the peripheral stimulation, certain aspects of lesions of the "optic" thalamus need be discussed. Dejerine with Roussy (1906) recognized that two kinds of syndrome result from hemorrhage into the internal capsule,—one, purely motor; another, mixed motor and sensory. The aftermath of the latter lesion he called the "syndrome thalamique." This comprises changes in superficial and deep sensibility contralaterally. Tactile, pain and temperature sensibility are diminished or abolished; and there are marked changes in the interpretation of the stimulus (dysesthésie, topoanesthésie, topanalgésie). The circles of Weber often increase. Bone sense is defective. All recognition of movement, active or passive, is so markedly diminished as to be almost absent. Notions of resistance, of force, of weight are totally wanting, and finally, severe pain and paroxysmal movements of the limbs and face on the side opposite the lesion followed a peripheral stimulus of this side.

Both Merle (1909) and Roussy (1909) described similar troubles following lesions in the lateral zone of the lateral nucleus. Head (1920), and with Holmes (1911), examined individuals with broadly similar lesions. The appreciation of posture and passive movement always showed the greatest loss. Tactile sensation was diminished, although generally a threshold could be established. Gradations of temperature were poorly discriminated, but heat and cold were never dissociated. Localization of a prick or a touch was very defective. However, if touch was present, a threshold could be established for the compass test. The sensation of prick was always present, though often less plain, and was interpreted as painful whether or not a violent muscular paroxysm

followed. Thus, irrespective of muscular response, this particular stimulation evoked an appreciation out of proportion to the stimulus given, and carried an affective quality never present on the normal side.

Lesions about the lateral part of the lateral thalamic nucleus cut off the ascending fibers to the cortex and leave that nucleus independent of cortical activity. Since the results of such injuries remain constant for years, it is possible to believe that they indicate in a degree the kind of appreciation of somaesthetic sensibility of which the thalamus is capable. The studies of such conditions have been summarized by Head from his point of view, and offer an interesting comparison with loss in the somaesthetic cortex. Proprioceptive sense is, in the "syndrome thalamique," most grossly affected; tactile and temperature discrimination (epicritic sensibility) are diminished and poorly localized. Protopathic sensibility (prick-pain and the extremes of temperature below 20°C. and above 50° or 55°C.) is generally left. Strong motor reactions and an excessive affective quality characterize the syndrome. When a stimulus is appreciated at all, a definite unvariable threshold, although raised, may be established. And appreciation is given with little or no hesitation, no sense of failure and no fatigue.

The injuries to the cortex studied by Head were delimited on the surface of the brain at the time of removal of skull fragments or bullets, or at a subsequent operation for herniation. For Bénisty's material the lesion was located on the brain by a system of projection of cortical convolutions upon the outline of the skull developed by French clinical neurologists under the guidance of Pierre Marie.

In a small circumscribed injury to the upper middle postcentral convolution Head reported (no. 3) that the most severe loss was found on the last two fingers. Measured passive movement was grossly misjudged over fingers four and five; slightly over two and three. Although localization of a point touched was but slightly affected, the awareness of three dimensions was wanting in all five fingers. The appreciation of texture was perfect over fingers one and two, defective over three and poor over four and five; that of form was lost only on the last two digits; that of weight was defective on the third and grossly affected on four and five. In similar lesions Bénisty found (ob. 1, 3, 5) that sense of attitude and stereognosis were abolished. Injury to the foot of the postcentral gyrus (Head, no. 1, 13, 18) spread these same defects over the first two or three fingers, and, in addition, tactile sensibility suffered. In lesion of the paracentral lobule or the upper postcentral gyrus these

defects were distributed over the foot. Bénisty outlined a similar peripheral distribution of loss from similar lesions. A small injury to the supramarginal gyrus (Head, no. 10 and 23) resulted in a great diminution of tactile sensibility and a raising of the threshold to superficial pain on the hand, especially over the radial half, with a marked hypotonia (no. 23). Now the cortical lesions reported by Bénisty were larger and involved areas which, in Head's cases, remained intact. Nevertheless, when the lesions coincide, there is a striking similarity in the parts affected. Injury to the superior part of the postcentral convolution shows a sensation-loss in the foot. The remainder of this gyrus is disposed in longitudinal bands, injury to which affects, in particular, the digits of the upper limb. The upper part (cubital or C_8 of Bénisty) is related to the fourth and fifth fingers, the next band, (radial or C_7 of Bénisty) to the remaining fingers in order, third, second and thumb.

Roussy and Branche (1919) reported a wound in the right parietal lobe, without exact localization, from which only the left hand suffered sensory loss. Here the greatest difficulty was experienced with the position of the fingers, although there was some diminution in pain and temperature-awareness and a loss of tactile sensibility. In another injury to the temporo-parietal region, besides the presence of what they call "sensory aphasia," deep sensibility and stereognosis were entirely absent; and tactile, pain, and temperature sensibility were lessened. They concluded, moreover, that cortical sensory disturbance could be differentiated from that of thalamic origin since the results of test varied in the former directly with attention. Further, the estimation of the intensity of the stimulus ("judgment" was the word they used) was inconstant and fatigue was rapid.

Guillan and Barré (1920) outlined the peripheral sensory loss from a lesion affecting the lower part of the upper half of the postcentral gyrus and the anterior part of the superior parietal lobule. An absolute astereognosis was present. Neither form, weight, volume nor consistence could be judged. Temperature was conceived with error in interpretation. Superficial sensibility was not affected, except that the circles of Weber were enlarged. The individual showed a "hypoalgésie" to prick, pinching and traction on the upper and lower extremities, but not on the neck and face. These three lesions correspond rather well with Head's report of loss in similar parts. But none of them support Bénisty's findings that general sensation on the opposite half of the body is deficient in lesions of the supramarginal and angular gyri and the

superior parietal lobule; that injury to the latter region affects the sense of orientation; and of the supramarginal gyrus, also the sense of attitude.

From Head's studies a glimpse may be gotten of the contribution which the intact somaesthetic cortex makes to the understanding of sensory stimuli. Apparently it provides for certain discriminative faculties, such as the appreciation of relationships in space, of the intensity of stimuli and of differences in weight, shape and consistence; and for integration this cortex is able, for example, to interpret the sensations given by a piece of tweed, not as roughness and thickness but as tweed; of silk, not as something smooth, but as silk. Fatigue and discouragement characterize its defective function, and under these conditions the threshold of stimulus does not remain constant. Moreover, hypotonia (noted also by Bénisty) is associated in distribution with the loss of appreciation of posture and passive movement. As in his early work upon cutaneous sensibility, Head makes the division into protopathic and epicritic moieties of sensation. And, seemingly, this is of real significance for the understanding of cortical activity. For it is protopathic sense which remains in lesions of the somaesthetic cortex, and protopathic sensibility, again, which is found present with lesions which cut off the lateral nucleus of the thalamus from this cortex. In these two conditions, the loss, which seems to represent cortical function, is in the epicritic variety of cutaneous sensibility and in proprioceptive sensibility.

The proportionate loss of these faculties has a certain relation to the position of cortical lesion. The further forward this lies in the postcentral convolution, and especially if it be also superficial in the precentral, the greater and more extensive the disturbance apparent in spatial tests. Judgment of weight and form is most severely injured by loss of tissue from the ascending parietal convolution. In a zone running backward across the foot of the pre- and postcentral gyri, over the supramarginal and angular gyri, tactile sensibility is mainly affected. And if the lesion is deep, discrimination of degrees of warmth is impaired.

The segmental distribution of parts of the body in the postcentral gyrus outlined by Head and Bénisty is corroborated by many others in such a definite manner that Goldstein regards this localization as fact and outlines it as follows: In the upper one-sixth of the convolution the foot is most dorsal; then come the leg, hip, and shoulder. The central two-thirds is the region for the hand, the ulnar division lying dorsal to the radial. In the lowest limit of the convolution lie the foci for the face and mouth. With Head, Goldstein believes that muscle

sense is affected not only by lesions in this convolution but also by those in the gyrus supramarginalis.

When, after severe injuries affecting one entire half of the body, there is a slight return of sensibility, this is to great pressure and to pain. In the young subject, Goldstein noted, return is for pain, for touch and for the extremes of temperature and without the ability to localize. Form, consistence and knowledge of movement remain grossly disturbed. This gives further support to Head's analysis: the protopathic moieties of sensation, alone, return.

Now when a certain area of the sensory cortex is injured Goldstein found, as did Head, that the different qualities of sensation suffer unequally. To begin with, Goldstein considers that the knowledge of movement, for example, is built out of the correlation of kinaesthetic and optic impulses, a "kinesthetic engramme." He believes that, in spite of severe impairment of muscle sense in the limbs, the site of movement can be identified if the "engramme" remains intact. Likewise a diminution in superficial sensibility impairs localization only in the sense that the localization fields are larger. Only if the relation of the superior parietal lobule with the optic region is destroyed, as in a lesion of the posterior part of the parietal lobe, then, in spite of intact sensibility, and even of intact automatic localization, is "conscious" localization damaged. Further, knowledge of objects may be derived by tactile sensibility. But in the appreciation of form and consistency deep sensibility also plays a great rôle. Hence, inability to apprehend tactile qualities need not prevent the knowledge of objects. Such useful objects as a watch or a key, for example, might be known by their form. In a like manner, glass or cotton could be identified, though form is lost, by pure tactile sensibility. Only the retention of the name and the ability to comprehend one quality is necessary. Consequently, Goldstein believes, it is essential to test not only for loss of the "pure" sensory qualities, but for the ability to integrate these, as well.

Goldstein agrees that lesions in the posterior central gyrus impair touch as a consequence of interference with sensibility, but that this is destruction of "pure" touch, he doubts. Touch, itself, seems to be especially inherent in the region of transition between the postcentral convolution and the parietal lobule. The quality of stereognosis, as related to touch, suffers, he finds, with injuries to the supramarginal gyrus (which he believes to be an area where the destruction of localization and of deep sensibility is combined with ataxia) and to the angular gyrus. Lesions of the latter, in his experience, give loss of

sensation, together with impaired ideation from the qualities of an object. In line with this is the lesion in the occupital lobe which results in his "Seelenblindheit." Further, Goldstein observed that muscle sense is embarrassed by lesions in the postcentral convolution and in the gyrus supramarginalis.

Gross destructive lesions of the latter area and of the gyrus angularis involving deeply the white matter, cause not only losses in muscle sense, general cutaneous sensibility and stereognosis similar to those following injury to the superior parietal lobule, but also disturb the recognition of objects by sight. Further, if the area of injury extends into the temporal lobe, auditory agnosis may be observed (Bonhoffer, 1915). When such an injury is bilateral, or sometimes when it is confined to the left parietal lobe (Liepmann, 1905 and 1914), all idea of the use of objects suffers severely. Gross losses on the right have been reported without any such sequelae (Brun, 1921). The severity of these symptoms may, however, be related to the grave subcortical destructions.

The neurological findings in Pfeifer's (1918) study of wounds of the head do not further solution of the mooted questions of the function of the somaesthetic cortex, as such, but they do contribute something to the association of injuries in large traumatic lesions of the parietal lobe. In all lesions of this lobe there was some destruction of body sensibility. In those which were situated toward its posterior division, the damage was almost entirely to cutaneous sensibility. Sense of position and of passive movement was destroyed in only two cases, and the loss in both these was associated with hemiplegia or hemiparesis. Weights were always distinguished as heavier on the affected side. Vibratory sense was often impaired over the opposite half of the body, and most severely in the fingers or the hand. For cutaneous sensibility, although a hemiaesthesia might be present, sparing a vertical median band on the trunk and sometimes on the face, the greatest loss was found distally in both the upper and lower extremities. Localization was never defective without at some time diminution or destruction of touch. Poor two point localization (circles of Weber) and inaccurate sense of weight were not associated with loss of sense of position or of passive movement or with astereognosis. Morphognosis and stereognosis were destroyed in but one instance (case 10) and that was definitely an injury to the area of transition between the superior parietal lobule and the occipital pole. Loss of prick-pain was often present with the other cutaneous losses, but no study of the threshold of stimulus was made.

In cases of one-sided sensory destruction a diffuse diminution in

muscular power was present with no sign of injury to the pyramidal system: no paresis, no changes in reflexes.

These generalizations of Pfeifer coincide at some points with Holmes' (1927) discussion of the disorders of sensation produced by cortical lesions. Like Pfeifer, Holmes finds that when the sensory loss is of hemiplegic distribution, the extremities are more affected than either the face or the trunk. Yet cutaneous localization, the compass test and comprehension of differences in weight are normally always vague and variable on the trunk, and possess little pathological significance until they are applied to the extremities. Holmes has investigated cases where disturbances of sensation appear to be more pronounced on the radial or ulnar half of the hand, but found no sharp line of demarcation between the normal and the anaesthetic divisions—the report which Head made. Thus, if the loss was great on the fifth finger, it diminished toward the radial half so that the index finger or thumb might be completely spared. In a like manner impaired sensation over the face, especially around the angle of the mouth, was found with that of the radial half of the hand, particularly the fingers. Holmes believes that the sensory zone is entirely posterior to the central gyrus; and, unlike Head (1920), that the sense of position suffers chiefly when the postcentral gyrus is injured. The recognition of form is found not only in the postcentral gyrus but also posteriorly in the parietal lobe. Tactile sensibility and localization also suffer with lesions behind the central fissure.

Some sensory functions, such as the identification of form, the discrimination of the simultaneous stimulation of two points, the comparison of weights, are more widely represented in the cortex than either tactile sensibility or the sense of position and passive movement. And yet it is the appreciation of movement, the recognition of its direction and amount, and the discrimination of weights which are most seriously affected by lesions of the cortex. In stationary cortical lesions complete insensibility to contacts with cotton wool or a camel's hair brush is not found, but to graded stimuli, such as von Frey's hairs or an aesthesiometer, reliable and constant evaluating answers may not be elicited. Holmes' independent observations agree with those of Head that if a lesion is indeed cortical, it is discrimination of the minor degrees of temperature difference which suffers; thermal sensibility as such is little impaired. Pain sensibility is the least affected. When the lesion is stationary there is no raising of the threshold to prick or other painful stimuli. Nevertheless, there is on the normal side a better apprecia-

tion of the form in which the painful stimulus is evoked. Holmes would explain the reports of analgesia in cortical lesions, either by the presence of a subcortical lesion, of an unrecognized hysterical anaesthesia or of a subjective disturbance.

A particular order of sensory loss with cortical lesions is now, indeed, so generally recognized that Piéron (1923, p. 97) in a discussion of the relative loss of sensibility has given to each moitie a coefficient ranging from 1 to 5 (1 is normal; 5 is total loss) as follows: heat and cold, 3.21; pain, 3.35; tactile localization, 3.38; vibration, 3.47; deep pressure, 3.54; superficial touch, 3.60; estimation of weights, 3.75; sense of attitude, 4.0; and stereognosis, 4.13.

It is difficult now to evaluate a case of dissociated monoplegia in which somaesthetic sensibility suffered in the reverse order, which was reported by Dejerine and Mouzon (1915) as a new type of syndrome of the sensory cortex. The wound in the left parietal region was small and circumscribed, but not localized upon the surface of the hemisphere. Prick-pain, temperature and vibratory sense suffered most, while localization and discrimination of touch, sense of attitude, of pressure, stereognosis and motor coördination were almost entirely intact.

There are certain kinds of injuries to the sensory cortex, such as tumors or vascular disease, which act in a manner reminiscent of strychninization of the cortex, and in some way excite special varieties of sensation. The aura of "pins and needles," not far removed from pain, preceding an attack of Jacksonian epilepsy, the continued sensation of cold which may be corrected by layers of flannels, are examples of dysaesthesiae recently discussed by Wilson (1927). Foerster (1926) has outlined in the postcentral gyrus and the remainder of the parietal lobe, the site of aura related to the various parts of the body. And for postcentral gyrus he has transferred the ladder form of motor localization across the central fissure.

On the contrary Cushing's figure 2 (1909), which outlines on the postcentral convolution the areas yielding sensation in the index finger and on back of the hand by electrical stimulation of that gyrus, falls in, not with the ladder type of peripheral localization in the postcentral gyrus, but rather with that plotted by Head, Bénisty, and Goldstein from lesions. In Cushing's first figure the localization of sensation in the hand and little finger was nicely confirmed by sensory loss in those parts following a single longitudinal cut into the tissue of this cortical area. It is interesting, moreover, that stimulating the foot of this gyrus

aroused a sensation of warmth. This is the area, in lesion of which Head found the greatest change in temperature discrimination.

Cushing's work was extended by van Valkenburg's (1914) study of like stimulations preceding the removal of small areas of the postcentral gyrus in two patients. Separate spots were localized for sensation in the individual fingers, and about the corner of the mouth and in the upper and lower lips. In the first case $\frac{3}{4}$ ccm. of cortex containing the spot which on electrical excitation gave paraesthesia in the little finger was excised. In the second the primary "paraesthetic" center for the corner of the mouth was removed (about $\frac{1}{2}$ ccm.). The sensory loss was definitely localized in the first case on fourth and fifth fingers of the left hand; in the second in the region of the right corner of the mouth. Six months later, however, the loss in the first was not entirely confined to the fourth and fifth fingers but had spread a little onto the contiguous palmar surface of the hand. The order of sensory loss in this case was considered typical. Severest was that of passive movement, two point discrimination, touch by tactile hairs, and temperature discrimination. The form, size, and consistency of objects were not recognized on the cubital half of the hand, but were on the radial. A certain ataxia was present. Pain-prick, strong pressure, the extremes of temperature remained, together with correct localization of all sensory stimuli. Such a case has all the aspects of an experiment, a definitely localized lesion, well studied; but its subsequent analysis was unfortunately interrupted by the patient's departure for America!

In this same communication van Valkelburg reported that stimulation of the "lobus parietalis" was not perceived. This region certainly cannot be field 7, which gave Foerster contralateral movements of the leg and arm, becoming eventually clonic epileptiform seizures. It probably was the inferior parietal lobule which gave no results.

Generally there is no functional compensation for loss of the somaesthetic cortex; investigators report no improvement. But only one, to the reviewer's knowledge, has attempted to train a patient in the localization of stimuli applied to definite spots. Graham Brown (1916), from such a study on an affected hand, concluded that there was improvement, and, further, that this could not be ascribed to the disappearance of the "confusion" error as can the improvement in the localization of untrained spots. But certainly the results of the training were not great enough to warrant therapeutically the time spent in attaining them. The contribution, however, shows that even a serious attempt to retrain localization after lesion in the somaesthetic cortex

does not yield results in performance at all comparable with those possible after loss of the motor cortex.

Recapitulating, Goldstein's observations are not at variance with those of Head. The men differ chiefly in their approach to the analysis of the material. Head does not use the term "Engramme;" Goldstein's point of departure is not the distinction: epicritic-protopathic. The abolition of what Goldstein calls "pure" tactile sensibility follows lesions similar in location to the lesions in Head's more severe cases of tactile impairment. Such involved the foot of the postcentral convolution, running posteriorly across the base of the parietal lobe. The damage to tactile sensibility found in injuries to the postcentral gyrus is evidently similar to that in Head's report for the same convolution. Both writers, however, describe greater difficulties with sense of position and of passive movement for lesions in this area, and especially with the understanding of differences in weight, texture and form. Head alone reports changes in knowledge of passive movement with superficial losses in the precentral gyrus. Yet Pfeifer described impairment of sense of position and of passive movement associated with paralytic or paretic symptoms, and with trifling implication of other components of sensibility. Pfeifer's finding of astereognosis with lesion in the area of transition between the superior parietal lobule and the occipital lobe coincides at no point with Bénisty's report of its presence in injuries to the pre- and postcentral convolutions and the supramarginal and angular gyri. Nor does the loss of sense of attitude with lesions of the supramarginal and superior parietal lobule correspond to the distinct hemianaesthesia without loss of proprioceptive sensibility reported by Pfeifer following injury to these same regions.

These are discrepancies. Yet whatever the conclusion about the exact range of somaesthetic sensibility which is located in the postcentral gyrus, the facts observed about the localization of peripheral parts in this convolution are very nearly in agreement. This localization is not of the exact ladder form found in the motor cortex; rather, the extremities are more largely represented; and, of the tissue assigned to them, the hand has acquired the major part.

Certainly this presentation has demonstrated that the aspect of body sensibility which generally suffers the greatest change following loss of tissue of the sensory cortex is not the crude recognition of touch, pain, temperature and pressure; but rather the awareness of spatial relations, the sense of position and passive movement, the appreciation of size, shape, weight and texture independent of their tactile qualities and the

evaluation of graduated intensities of stimulation. Sensation to prick, to vibration, to extremes of temperature and the gross recognition of a tactile stimulus without exact localization are least likely to be damaged by loss of this cortex.

It is then the more complex aspects of somaesthetic sensibility—whether of the general cutaneous or of the proprioceptive variety,—which suffer more severely. Using Stopford's extension of Head's hypothetical dual mechanism, it is the epicritic division rather than the protopathic, which tends to show the greater loss.

A more complete conception of function of the supramarginal and angular gyri and of the areas bordering the arbitrary divisions of the parietal and occipital lobes will emerge from the discussion of injuries to the occipital lobe and in the consideration of the subject of aphasia.

THE OCCIPITAL LOBE. The occipital lobe has been divided into three regions, distinguished by peculiar cyto-architecture. The area which surrounds the calcarine fissure in man and anthropoid apes is now generally accepted as the sensory projection field for sight (area striata, field 17 of Brodmann, the calcarine cortex of Campbell, O. C. of Economo and Koskinas). Surrounding the calcarine cortex lies the visuo-psychic cortex of Campbell, which covers, in his classification, the remainder of the occipital lobe. In that of Brodmann or Economo and Koskinas two varieties remain. The first surrounds the visuo-sensory or calcarine area concentrically (field 18 of Brodmann, area parastriata of Economo and Koskinas); the second stretches out to the boundaries of the lobus-occipitalis (field 19 of Brodmann, the area peristriata of Economo and Koskinas).

Considered cytologically, the area peristriata is probably an associational region for sight, while the area parastriata because of its giant pyramids has been thought by Economo and Koskinas to be an optic-motor region. In the following discussion, the evidence for difference in function, accompanying that of structure will be given. Such a division of the occipital lobe takes for granted, at the outset, that there is no confusion in the localization of the primary center for sight in the cortex. It is interesting, therefore, to find Mott, in 1907, practically apologizing for his belief that the visual cortex is limited by the distribution of the line of Gennari in the depth of the calcarine fissure. The cause for that apology lies in the early attempts to localize the center for sight; sight centers were strewn along the lateral surface of the hemisphere, in the supramarginal gyrus and the frontal lobe as well as in the occipital. And, according to some, the destruction of the whole occipi-

tal lobe was necessary for loss of sight. The investigations upon injury to this region in recent years explain the confusion which permeated these analyses of the areas involved in cortical vision.

Hitzig's (1874) announcement that lesion of one caudal part of the dog's hemisphere was followed by blindness in the opposite retina was followed by that of Ferrier (1876) that the cortical center for sight was localized in the angular gyrus of the monkey and in homologous regions in the brains of dogs, cats and rabbits. Shafer (1888) removed both angular gyri in a monkey. For a few days the animal appeared totally blind. Later he could see small objects at a distance, for example a raisin, but, on running up to it, had great difficulty in finding it. Munk (1877–78 see, 1890) maintained that, after bilateral removal of a certain area "A" in the dog's occipital cortex, the animal could see, but not recognize, objects, —"psychical blindness." It had "visual sensations" only. But were the whole of the occipital lobe bilaterally ablated, blindness was absolute and permanent. He found the same to be true in monkeys. Luciani, with Tamburini (1879), thought they had demonstrated that the visual cortex in dogs is not restricted only to the occipital lobe, but that it spreads forward on the lateral surface of the hemisphere as far as the frontal region. And that in the monkey, the hemianopsia which results from unilateral removal, not alone of the occipital lobe, but also of the angular gyrus, is not permanent. Luciani and Seppilini (1886), in their researches attempting to substantiate Munk's theory of the projection of the segments of the retina upon the occipital cortex, found that visual disorders occur in dogs also after removal of the frontal area. But Luciani says that the disorders following removal of the frontal and temporal regions are but temporary whereas the losses resulting from ablation of the parietal and occipital areas are permanent. He believed that this demonstrates that attempts to place vision in the occipital lobes are but speculation.

Later, both Tschermak (1905) and Kurzveil (1909) repeated these experiments and found, on the side opposite an occipital lobe ablation, hemianopsia and changed eye reflexes, which persisted, in the experiments of the latter, for more than a year. Also they found degeneration of fiber tracts to the subcortical centers for sight. Minkowski (1911) reported that bilateral removal of the area striata produced permanent blindness with loss of all ocular reflexes except those of the pupil. Luciani again removed this region in the dog, but incompletely as shown by autopsy. The animals never stumbled against chairs or other obstacles put in their way; they were then not blind; and never

became blind unless the thalamic centers of sight were also removed (Lo Monaco, 1910). Ferrier described something similar for Macacus rhesus. A temporary amblyopia gives way to what might be called psychical blindness. This residual disorder becomes aggravated upon injury to the gyrus angularis.

A more unsatisfactory condition cannot be imaged. The area striata, outlined for the macaque by Brodmann (1909) and for the dog by Campbell (1905), receives fibers from the thalamic centers of sight, but, apparently, is not physiologically comparable to the histologically homologous area in man. Besides this circumscribed region of the occipital lobe, the angular gyrus in monkeys, and the frontal region in dogs have been assigned a part in cortical vision. Although histologically homologous, the area striata has not, however, attained to the degree of specialized development characteristic of this area in the brain of man. It is therefore reasonable to consider that function may not be strictly analogous in the three species. It is not impossible that the thalamic centers for sight may serve as a more complete mechanism for the lower animals. The fact that the dog is not blind when the area striata is removed does not mean that it is not the cortical center for sight reception (degeneration experiments have proven that it receives the optic radiation) but simply that it does not function as does the homologous region in man.

Confusion as to the localization of the primary cortical center for sight has also characterized the work on man. Henschen (1892) maintained, on the basis of his clinical and pathological studies, that not only was the visual area restricted to the narrow limits of the cacarine fissure, but also that the retina was projected upon it in an orderly manner. The upper quadrants of the retina were located in the depth and surface of the upper lip of this fissure and the lower quadrants, in its lower lip. Dejerine (1893) allocated to the primary visual center the whole of the mesial surface of the occipital lobe. But even he did not spread this region as did von Monakow (1900a and b), who thought it included not only the calcarine cortex, but the whole of the mesial and the lateral surfaces of the occipital lobe and a part of the gyrus angularis, as well. Inouye (1909) described a case of injury to the end of the occipital lobe, substantiating Henschen's analysis. He believed that there must be a primary sight area with sharp projection, and a nearby region for the remainder of the sight function. In his analysis, von Monakow does not ascribe to destruction of the area calcarine such limited or constant effects. Destruction of the dorsal or ventral lips

of the area striata, or of both, yielded either total hemianopsia, or quadrant hemianopsia, or no hemianopsia with only a loss of color vision. He considered the sight cortex, rather, an organ for the higher evaluation of sight stimuli, acting in its entirety as a part of the whole mechanism which analyzes light sensations; and he did not find within it parts separated for the awareness of light, color, form and residual visual memories. He also thought of this region as closely connected with neighboring eye-movement areas for spacial orientation. Therefore, one would not expect him even to consider further localization for the macula within the area striata.

That macular vision is often spared in bilateral hemianopsia due to lesion of both occipital cortices, led von Monakow to express the opinion that central vision is not represented in the area striata, nor, perhaps, in any particular part of the cortex. It has been suggested (Wilbrand, 1907) that each area is bilaterally represented; that connection of the two sides through the corpus callosum allows for its escape (Lenz, 1909). Again, the macula might be represented diffusely (Sachs, 1897), or spread diffusely in a horizontal layer throughout the area striata (Goldstein, 1917), or lying along the bottom of the calcarine fissure (Bolton, 1915). More recently, however, Inouye (1909) brings evidence, from wounds of the occipital lobe in the Russo-Japanese war, to show that the macula must lie in the posterior part of the length of the fissure. And finally Lenz (1914 and 1924) in a review of this question says that although some reported cases are seemingly against it, nevertheless there are many which support such posterior end representation. He agrees therefore with the later conclusions of Henschen (1913).

Grünbaum and Sherrington (1902), and later Leyton and Sherrington (1917) found two regions in the cortex of anthropoid apes which, upon stimulation, give movements of the eyelids and eyeballs. Peculiarly enough, the areas for opening the eyes and for closing them are widely separated. The latter is found in the genu inferior of the sulcus centralis, a neighbor to the region of the thumb and adjunct to those areas which result in movements of ear, nostril, neck and lip. Closure of both eyes results, but that of the contralateral is always more vigorous. Opening of the eye occurs with a certain regularity from stimulation of an area in the frontal lobe anterior to the interior division of the gyrus precentralis and again in the occipital pole about the area striata. Closely associated with this movement from the latter region, is turning of the eyeballs toward the opposite side. The reacting points are most numerously distributed along the gyri that border the calcarine

fissure at its posterior pole. The frontal region is a large one, bordering the middle and inferior frontal convolutions. The opening of the eyes is associated, generally, with conjugate deviation of the eyes to the hetero-lateral side; sometimes with movements of convergence and sometimes with a movement upward and inward. The lateral deviation may be slightly modified partly downward or upward.

Similar stimulation of the mesial surface of the occipital lobe in man (Krause, 1924; Löwenstein and Borchardt, 1918) does not result in movements of eyelids or eyeballs, but, rather, in sight phenomena such as stars, twinkles, toothed rings and light sensations (photosien). When stimulation is extended further over the cortex of the occipital lobe, optic hallucinations appear. Förster (1926) believes that epileptiform attacks which are preceded by movements of the eyeballs have their foci in the mid-central area of the second frontal convolution. Brodmann (1914) says, however, that it is possible to have a lesion in the vicinity of the sight center (its lateral surface), which disturbs conjugate deviation, destroys accommodation and looses fixation; and with or without injury to sight as such. In a unilateral destruction, conjugate deviation of the head and eyes is to the side of lesion. Such lesions are generally deep and destroy not only cortex but also white matter beneath. And they are often accompanied by some aspects of asphasia.

von Monakow (1914) found that one-sided lesions in the gyrus angularis result, not only in hemianopsia, but also in impairment of eye fixation, accommodation and space orientation, and often in ptosis. Such loss would be capable of many explanations; perhaps tone is less in one set of muscles, due to the one-sided loss of retinal images; or there may be paralysis of the opposing muscles, or, finally, it may be the result of loss of muscle sense. The first is easily answered; there may be no loss of tone in the blind. As for the last two: von Monakow thinks that the coöperation between the innervation of the extrinsic eye muscles and of the muscle of accommodation, together with their kinaesthetic sensibility has been disturbed. It is possible, however, that either one or the other may be the important factor.

Marie and Chatelin (1915) made a careful comparison of the losses in the visual fields dependent upon the destruction in the occipital lobe made by the passage of projectiles through the posterior pole of the cranium. The probable site of such injuries was projected upon charts made by Marie, so that the cortical loss was at least approximately localized. After commotional phenomena had subsided and the extravasated blood had been absorbed, the field losses remained circum-

scribed and constant. They conclude that the cortical center for sight is in the calcarine fissure itself and the two adjacent gyri, the inferior gyrus of the cuneus and the superior gyrus of the lobus lingualis. A superior quadrant, right or left, of the retina is localized in the superior half of this region, on the same side; hence, an inferior quadrant hemianopsia was found in the upper lip of the opposite fissura calcarina. And in like manner, superior quadrant hemianopsia was correlated with destruction of the under lip of the opposite area striata. They further correlated loss of macular vision with wounds of the posterior tip of this area. On the other hand, if the wound was confined to the anterior division of the fissure the scotoma was always peripheral in the visual field.

In the next year Holmes and Lister studied the same type of lesion in wounded men. Many of their studies were subsequently checked by autopsy. They reported, without knowledge of the work of Marie and Chatelin, the same results; namely, that the lower half of the field of vision is represented in the dorsal and the upper half in the ventral lips of the visual areas; that central vision lies in the posterior extremities of the area calcarina, probably in the margin and extending slightly onto the lateral surface of the occipital pole. The periphery of the retina is probably represented toward the anterior part of the area striata with concentric zones lying between the periphery and the macula, represented in a linear manner passing from the anterior to the posterior part of the calcarine fissure. Later, Holmes (1918) has outlined, upon the area striata, the projection of the retina (fig. 16, p. 383) in such a manner that one concludes that approximately one-fourth of the posterior region surrounding the calcarine fissure is the cortical area for central vision. They find that the macula is not bilaterally represented and explain its frequent intactness in civil lesions to a peculiarity of the blood supply of the mesial occipital pole. Beevor has described, in some 10 per cent of cases, an overlap of the posterior cerebral artery onto the region generally supplied by the middle.

Goldstein (1927) substantiates in part, apparently without knowledge of it, the work of both the French and English neurologists on this cortical region. He concludes that the cortical destruction of visual fields is dependent upon injury to the regio calcarina. A hemianopsia is the result of a complete lesion in one hemisphere; an inferior quadrant hemianopsia, of lesion in the upper part of the calcarine area; a superior quadrant, of one in the lower part. Peripheral scotomata are connected with injury to the anterior division of the area calcarina.

He does not at present seem convinced that the cortical loss of central vision is dependent upon lesions of the posterior part of this same area, although he is cognizant of the work of Sänger (1918) who thinks that the fiber bundles for the macular region end in broad fashion at the posterior pole. Wilbrand (1917) and Sänger (1918) find that a retinal loss in a horizontal meridian of the retina is dependent upon a lesion at the bottom of the fissure and in a horizontal line, upon one on the gyri, —exactly the projection given by Holmes (1918) for these same regions.

In the studies made by Holmes, there was no specific loss of color vision. No disturbance of color was found where the visual acuity for white or black was also not lessened. What hemiachromatopsias he found were also instances of hemiamblyopia. On the other hand Goldstein finds that color vision may be impaired with completely or relatively intact sensibility for black and white. Gelb (1918) reports an individual instance in which there was 6/10 vision in both eyes and at the same time a complete color blindness, persisting for a year. At the end of this time the patient thought himself normal, but when he was tested with the spectrum, considerable deficiency was found; the violet end was markedly affected, and all colors were paler, and lacked the depth visible to the so-called normal eye. At first, he appreciated blue and yellow best; red and green were paler and without a corresponding depth. A dark piece of paper on a bright gave the impression of relief. Often the brightness of a color, as well as its penetrating quality was interpreted as thickness and height. Goldstein (1918) commented upon this presentation by saying that red-green blindness was relatively frequent in brain wounds. In none of the cases which either of these observers studied, was there a sector or hemianopsic destruction of vision. They were not lesions of the calcarine area. The majority of the lesions lay on the lateral division of the occipital lobe, and in Gelb's cases all were in the left hemisphere. Poppelreuter (1917) believes, from his data, that disturbance of color sense is better understood as weakening of an absolute color consciousness; thus, cases of hemiachromatopsia become hemihypochromatopsia, a loss of appreciation of intensity. And in this way he agrees with the conclusion of Holmes.

Riddoch (1917) studied the dissociation of visual perceptions due to occipital injuries. He found that some destructions of this region leave vision for movement and light stimuli only. Moving objects have no distinct form or color, rather they are like shadows. In three instances where vision for objects was recovered, the appreciation of movement

returned first, and its field was always the larger. The test objects used were generally white or black. Although he gives a chart of a visual field with markedly restricted areas for red and green, there is, unfortunately, no discussion of the color vision. But he did describe a patient who retained movement, form and color, but lost visual orientation and the recognition of depth. All objects were correctly named and described, but appeared the same distance away from him. Everything was perfectly flat; "a sphere is a circle; a cube, a square; a pyramid, a triangle;" a friend, an outline. The patient himself said, "Something else, that indicates depth, has been taken away." The former injuries, dissociating form and color from light and movement, were apparently restricted to the calcarine area. In the last lesion, Riddoch thinks that the optic radiations on the left were spared, with the greatest destruction in the polar region of the occipital lobe. The point of entry of the projectile must have been somewhere in the lower part of the inferior parietal lobule, and it is clear that Riddoch relates injury here with the impairment of visual orientation, and would, apparently, agree with Poppelreuter (1917) that destruction of direction is independent of field defects. Goldstein and Reichmann (1920), on the other hand, believe that there is a straight dependence. Certainly, instances of the persistence of a completely normal visual field when depth, direction, or distance has been destroyed are rare. Moreover, in such cases more tissue than that of the area striata has been injured.

Besides difficulties with perspective and distance, there are, generally, disturbed eye movements. And as all have been associated at some time or other with lesion of the lateral surface of the occipital lobe, or its immediate area of transition, it is not strange to find Sachs (1895) postulating an area for the movement of the eyes in the sight cortex. Förster (1926) has reported that stimulation of Brodmann's field 19 (area parastriata) gives deviation of the eyes to the opposite side. Defects, known as optic-motor nystagmus, resulting from injury to the posterior part of the head, have been associated with this area (Cords, 1926; Strauss, 1925).

In addition to the difficulties with orientation which accompany disturbance of eye movements, in general there is a gross loss of spacial orientation such that the patient loses his way in familiar surroundings. This loss may accompany gross or minimal restriction of the peripheral fields of vision. Lenz has suggested, in his review of the literature, that the right occipital lobe holds a greater meaning for this difficulty

than the left. This peculiar loss will be discussed with lesions in another part of the cortex.

Poppelreuter (1917) has studied, in great detail, the psychic upset caused by wounds of the head. His interest is mainly psychological, with little attempt to correlate the changes in phenomena with any definite areas of cortical lesion. Nevertheless, certain isolated losses are of interest. Binocular vision may fail, without visual agnosia or destruction of direction localization. The latter is relatively independent; it is found in both sound and unsound visual fields. Inability to grasp an object is rarely seen when free central fixation is present. When it is, Poppelreuter regards it as a detail of a general optic-motor uncertainty, and not as limited to the grasping of an object;—all direction is affected,—a destruction, rather, of the localization mechanism. This, he believes, occurs in double sided occipital injuries involving the white matter to a great depth. In his instances of inability to comprehend regularly grouped numbers or the form of things, hemianopsia (unilateral or bilateral) or hemiamblyopia were present. When one compares the protocols of injuries and the pictures of the wounds, the occipital lobe itself might not have been directly injured in one of these cases and in others there must have been wounds in the area of transition of the parietal lobe with the temporal or the parietal with the occipital.

However, for the consideration of our particular problem, localization, the reports of Riddoch (1917), Holmes (1918), Smith and Holmes (1916) and Holmes and Horrax (1919) are more pertinent. The materials of these are cases in which either the supramarginal or the angular gyrus was injured, often bilaterally. Naturally, either quadrant or half circular hemianopsia was present. Such cases of disturbed orientation and localization in space by sight can be roughly divided into those with and those without comprehension of the third dimension. Lesions affecting the gyrus supramarginalis (Holmes, 1918) and the underlying sight projection fields are followed not only by disturbances of orientation similar, probably, to the gross ones reported in Goldstein's review, but also by inability to estimate distance, either relative or absolute (Riddoch, 1917), and by failure to recognize the relative lengths and sizes of objects. These were accompanied by disturbance of eye movements and of ocular reflexes (the pupillary reflex excepted). Great difficulty was experienced in the fixation of objects, in following a moving or jerky object, and to converge and accommodate for near objects was impossible. No visual agnosia was ever observed. These individuals had difficulty in looking in a direction at command.

In the report of Holmes and Horrax, the wounded man could look as directed; and although accommodation for near objects was affected, he could converge on an object in his hand. But he collided with objects, although he saw them. He could never see but one side of a box; "his eyes couldn't get around the corner." He had no comprehension of the third dimension. There was in none of these cases loss of color vision or of the appreciation of differences in light and shade. The comprehension of depth is, then, dependent upon something other than the simple possession of binocular vision.

Certainly the area striata is now definitely proven to be the primary cortical center for sight. Injury to other regions may show changes in the complex mechanism of related sight phenomena, but not blindness, as such. And although we may be practically certain of the result of lesion in other loci, the disorders which follow cannot be looked upon, necessarily, as entirely the loss of function of that particular portion of cortex, but in part, perhaps, as disturbance of mechanisms of correlation. The simple anatomical point of view must give way to the physiological concept of a functioning whole, and yet we may believe, with Henschen, that the retina is represented on the cortex of man in as nicely a placed anatomical arrangement as one could wish.

Besides the more primary difficulties found in injury to the posterior portion of the hemisphere, the condition of visual agnosia, or psychic blindness (Seelenblindheit) may result. The individual does not know what he sees, and yet there is no change in the visual fields, in acuity or in the visual perception of color differences. Goldstein (1927) believes that such injury is often bilateral, but may be one sided, left sided in right handed individuals. In that way it resembles motor aphasia. Gelb and Goldstein (1920) published an interesting account of this condition: an individual who had not only what they called "apperceptive" Seelenblindheit but, also, astereognosis, disturbed localization over the entire body, and impaired execution of movement, as well as a certain disturbance in intelligence. Head considers this as descriptive of an aspect of aphasia.

But before that fascinating subject can be considered the cortical centers related to hearing must be discussed.

THE AUDITORY CORTEX. There is no difficulty in delimiting the small turned-in area in the superior temporal gyrus which receives the cortical radiations from the medial geniculate body of the thalamus (Flechsig, 1907). It covers mainly the transverse gyrus of Herschl, extending somewhat upon the inner surface of the superior temporal gyrus, and

corresponds rather well to the outlines made by Flechsig's myelinization studies. Campbell (1905), and Brodmann (1909) find, in Herschl's convolution and its neighborhood, two types of cortex, an anterior or inner and a posterior or outer. The inner can be cytologically differentiated from the insular type of cortex as well as from the temporal. Brodmann further divides, on cytology, the superior temporal gyrus into the area parainsularis (52), and the area temporalis transversa-interna (41) and externa (42). Economo and Koskinos divide the internal division of the superior temporal gyrus and the Herschl convolutions into three areas (TD, TC and TB). The middle outer third of the former gyrus, which surrounds these regions, is Ta, and is similar to Brodmann's field 22. TD lies over the two Herschl convolutions, at their transition with the parietal lobe (area supratemporalis simplex magnocellularis). It contains very large pyramidal cells in the lower part of its third layer. TB lies concentrically about TC and within TA, apparently similar to Brodmann's field 42. TC is the area supratemporalis granulosa (Brodmann's 41), classed by Economo and Koskinos as a Konio cortex, and characterized by small cells in all layers, a prominent granular IVth layer and a VIth layer with many polymorphous and pyramidal cells. This is the region which receives the majority of the thalamo-cortical radiations (Flechsig, 1907, and von Monakow, 1914). According to Brodmann (1914) Probst has found that the fibers from the inferior colliculus may be seen to enter the acoustic cortex after those from the medial geniculate bodies have degenerated. Winkler (1921) found, in a human brain of three months, two groups of fibers leaving the medial geniculate body, one which passes to the gyrus of Herschl and the other to the parietal lobe. In the first sheaf of fibers he has identified some coming from the posterior colliculus. Dejerine (1901) finds but the one sheaf, that destined for the temporal lobe. In no case of degeneration of the parietal lobe has he found changes in the medial geniculate body. There is little doubt, then, that a small area in the superior temporal gyrus running over into Herschl's convolution is directly connected with the subcortical centers for hearing.

There is greater difficulty in establishing homologies for the acoustic center than for that of sight. Brodmann did not find in the monkeys he studied (Cercopithecus) any region which could be cyto-architectonically thought homologous to the gyrus temporalis transversus in man (fields 41 and 42) or to other fields in that region (fields 36, 37, 38 and 52). The superior temporal gyrus (field 22) is, however, homol-

ogous to the same field in man. On the other hand Campbell "has satisfied" himself that the elevations which are found on the Sylvian side of the first temporal gyrus in the brain of the orang and chimpanzee are homologous to Herschl's gyrus. It is possible that this difference between primates exists, but one must not forget that Campbell did not see distinctions in cyto- or myeloarchitecture that were visible to Brodmann. Kappers (1921), on the other hand, from studying the gross homologies of this region, believes that Herschl's transverse gyrus is sunk for the greater part in all primates. If the homologies of this region are difficult to determine within the primates, they are even more difficult to establish between the primates and the subprimates. Kappers believes that the posterior limb of the fissura suprasylvia of subprimates is the equivalent of the fissura supratemporalis of primates, and that the anterior limb sinks into the island of Reil as in higher forms; which would make the gyrus below the suprasylvian fissure homologous with the superior temporal gyrus and the oldest part of the lobus temporalis. But in none of the primates or subprimates studied by Brodmann was an area resembling the acoustic cortex discovered. The area which was apparently homologous was the outer part of the superior temporal gyrus (field 22).

This lack of knowledge of homologies may account, in part, for the discrepancy in the results of attempts at experimental ablation of the hearing cortex. Or the exactly corresponding region may not exist. Further, the lateral lemniscus is not a completely crossed system. Neither Ferrier's (1876) report of deafness following removal of the superior temporal gyrus in Macacus rhesus nor Munk's of ablation of the lobus temporalis in dogs withstood the criticism of repetition by Luciani (1879 and 1885) and his assistants. Luciani's extensive bilateral extirpations of this region in dogs gave severe affection of hearing, but never complete deafness. After shock had disappeared, only a partial "psychical" deafness remained; the animal failed to appreciate the significance of sounds, but apparently heard them. Ferrier (1890) repeated his earlier bilateral ablations of the superior temporal gyrus on a "dog-faced monkey." Reactions to sounds were not entirely abolished, but the animal remained indifferent to those which previously had held meaning of the approach of delicious morsels of food or of friendly attention. It is difficult to believe Larionow's (1898) projection of the cochlea on the hearing cortex. He reported that in the dog the perception of low tones was located in the gyrus suprasylvius posterior; that of middle range, in the gyrus ectosylvius posterior; and that of

high tones in the gyrus sylvius posterior. Goltz's cortex-free dog was awakened by a horn blown near his ears.

To establish clinically a definite function for the circumscribed acoustic projection area of man is almost impossible, because the lesions recorded have not confined their radius of injury to this cortex. von Monakow (1914) believes the perception of sound to lie especially in the posterior two-thirds of the first temporal convolution; Dejerine and Serieux (1897) in its anterior part; Bechterew (1899) spreads it out even into the middle temporal gyrus; while Mills (1891) believed that the destruction of the two upper temporal gyri of both hemispheres was necessary to complete brain deafness. Mott (1907) described an instance of bilateral injury to the auditory centers in which the individual was absolutely deaf, and could understand written words and phrases only if they were simple. The lesion in this case was destruction of the posterior third of the first temporal gyrus, of the transverse gyri of Herschl and of the posterior part of the second temporal convolution. Even Campbell's case of a man born deaf was not a restricted lesion, for not only were "exquisite" changes found in Herschl's convolution, but also others, spreading over the posterior part of the insula and the "psychic" field of the superior temporal convolution. Nevertheless, there is no case of bilateral destruction of Herschl's convolution in which hearing is not markedly damaged (Goldstein, 1927). Last year, however, Dandy removed the right cerebral cortex almost completely (the medial surface remained). The patient lived about five months. She was tested by Guild and, in spite of the loss of all three gyri of the temporal lobe, was able to distinguish pitch in the left ear.

The areas lying contiguous to the auditory center, especially the posterior third of the superior temporal gyrus, are often implicated in the processes of verbalization. It is especially interesting, however, that large tumors of the right region in right handed individuals have been described without any apparent symptoms (Oppenheim).

Pfeifer (1921) has recently collected all the material which points to a representation of the cochlea on the hearing center. He finds a marked difference in the development of Herschl's convolution and the superior temporal gyrus in individual brains. In some instances he has correlated enlargement of these areas with musical ability. He believes from certain circumscribed lesions reported that the tones of greater frequency are appreciated in the medial division of the hearing center (the root of the convolution on the side of the Sylvian fossa) and those of less frequency in the lateral part, i.e., the outer convexity of the first

temporal gyrus. Two years later with Quensel he reported that in lesions of this region musical notes may be heard as noises only. And Henschen (1926) has found cases where "music blindness" exists without "word blindness." At present the data presented are suggestive, but not abundant enough to be stated as a fact. And yet these claims for cochlear representation in the cortex and for "music deafness" do not extend beyond the boundary of the upper temporal convolution. What contributions other portions of the temporal lobe make to the activity of man is not known. The two superior temporal convolutions on the left (in a right handed individual) are apparently important in certain phases of the clinical entity known as aphasia, and will be discussed in that connection.

CORTICAL AREAS CONCERNED IN VERBALIZATION. The partisanship and emotional reactions which have clouded the attempt to localize and analyze the disturbances of verbalization consequent upon cortical injuries can be understood by the historical consideration of this subject given so superbly by Head in the first one hundred and fifty pages of his two-volume discussion of the subject. It is, therefore, with no little temerity that the reviewer attempts a discussion of the recent contributions to the subject.

Broca's communication (1861) that aphemia in the patient reported "was the result of a profound but accurate circumscribed lesion of the posterior third of the second and third frontal convolutions" produced no small stir among neurologists and medical men alike.

While Broca was being forced to debate the subject of localization with lecturers and clinicians in Paris, Hughlings Jackson was studying the defects of speech dependent upon cortical injury. His contribution to the elucidation of the subject had little effect upon its subsequent development. The difficulty of reading his papers, filled, as they are, with qualifications of any generalization which he made, and their inaccessibility to clinicians on the continent, may be the reason. Anyone reading them in their reprint form (Brain, 1915, and Neurological Fragments, Oxford, 1925) cannot help but be startled by the clear-cut distinctions which they hold. Jackson continually insisted that the motor difficulties due to paresis of the muscles of speech must be separated from true disturbances in speech itself. Here, also, one may read of his classification of language into intellectual or propositional and emotional. When propositional language suffers, all aspects of expression, not only the use of words but also writing and the conveyance of meaning by signs, are impaired. • Those which are the more highly

developed suffer most, and the less highly, the least. Emotional language is conserved in such a manner that gestures, facial expression and the habitual emotional words, swearing and ejaculations, are retained, to be used when justified, although after the occasion has passed not one of the words can be repeated. It was not sufficient for Jackson to record that a man was speechless; he had to know in what degree and how his intelligence had changed. Jackson put down what a patient could do and allowed him ample apportunity to express his understanding in any way that was possible for him. Further, Jackson did not consider a destructive lesion the source of abnormal activity in the patient, but rather that "positive mental symptoms arise during activity of lower centers or lower nervous arrangements which have escaped injury." The lesion is not a stimulus: it is a destruction which affects more complicated processes first and reveals the less complicated. The conception which he held was physiological and psychological. He made no attempt to consider affection of speech as the simple result of a lesion in a circumscribed area; for example, inability to understand a written word as a lesion in the visuo-psychic area or the non-comprehension of a heard word as one of the auditory psychic cortex.

Wernicke (1874), reasoning in the latter way, outlined on the first temporal convolution a center for the understanding of the spoken word. This "sensory" aphasia is distinguished from the aphemia of Broca by the ability to say words and the lack of comprehension of the spoken word. In Broca's "aphemia," on the other hand, the patient cannot speak, he is dumb, but he understands what is said to him. Dejerine (1884) added to this an area (the meeting point of the occipital, temporal and parietal lobes) by whose destruction the patient was unable to read (alexia), but could say words and recognize them when they were spoken. Thus, word-blindness and word-deafness came into being.

Lesions in Wernicke's area for sensory aphasia were isolated by Henschen in his attempt to circumscribe the receptive center for hearing. He confirmed Wernicke's conclusion that lesion of the temporal gyri, especially on the left, was responsible for the loss of comprehension of spoken words, i.e., word-deafness. He located word-blindness in the angular gyrus. Injuries of the occipital lobe, other than of the calcarine fissure, gave various degrees or kinds of visual agnosia. The patient might not be able to understand the use of an object he saw; he might not comprehend the meaning of words or letters; or he might not be able to write. Continuing in this manner, Henschen dotted

the cortex with centers: for appreciation of figures; for reading; for writing; for the comprehension of music; until his serious and laborious attempt to discover correspondence between symptom complex and site of lesion reduced itself to absurdity.

And it is with some relief that we turn to von Monakow (1914) and his diachisis. von Monakow recognized clearly that following all injury to nervous tissues, there is, first, a stage of shock, then, the passing of this with the manifestation of activity on the part of the remaining nerve cells, and lastly, the stage of further recovery or compensation. In this manner, after diachisis has passed, the recovery proceeds to a certain stage which becomes more or less stationary, and presents the permanent disintegration.

In such a complex act as that of the presentation of propositions either in spoken or in written language, there must be certain rhythms of excitation and motor response taking place in a definite time sequence. To von Monakow, "motor" aphasia is a change in performance, both external and internal, such that the patient can only express himself emotionally or be able to write such primitive words as his name. And commonly, although the patient may recover his ability to understand an ordinary conversation, a more involved logical argument will be beyond him,—a difficulty which had been assigned to the field of "sensory" aphasia. Throughout, emotional expressions flow easily; short sentences may be said with some ease.

In von Monakow's "sensory" aphasia, the afflicted man can not follow an ordinary conversation; he may be unable to do as commanded; and yet he may comprehend such simple questions as, "How are you?" "How old are you?"—questions which the average adult asks of children. In contrast to the motor aphasic, he may speak fluently, but unless he confines his speech to the conventional forms of phrasing he commits grave errors in the use of words. His accent, inflection, intonation, together with his speech rhythm, are grossly modified. His mistakes in writing bear a certain resemblance to those he may make when reading or speaking. And, according to von Monakow, these two "pure" types may be mixed.

The "motor" type of aphasia appears when the posterior portion of the third frontal convolution, or its underlying or surrounding parts are injured. The greater the extent and depth of the lesion, the more severe will be the symptoms. Yet if the patient suffers no further diachisis it is possible for a degree of recovery to supervene that will at autopsy provide a grave discrepancy between lesion and symptom.

The converse can be seen in those instances when death comes before diachisis has passed; the symptoms then will be graver than the apparent lesion warrants.

The "sensory" type of aphasia can be produced by lesions anywhere in that band of cortical tissue which stretches across the upper temporal convolutions to the angular gyrus. Injuries in the occipital region, besides the frequently accompanying hemianopsia, manifest themselves rather as difficulties in visual orientation. von Monakow's study follows in a certain way the crude path made by Broca, Wernicke and Dejerine. Yet, although he found that certain lesions were closely connected with rather definite disturbances in external and internal formulation and comprehension, he did not locate centers as such on the surface of the cortex in these regions. The difficulties which he described he interpreted as more closely correspondng to diachisis, its severity and its duration. It must be remembered, however, that von Monakow's data were gathered in general from lesions secondary to disturbances of blood supply; that many of his patients suffered from large areas of cortical destruction, and that frequently the lesions penetrated deeply the white matter.

In 1906 Marie published a re-examination of the two brains which Broca had used to establish the causative lesion in loss of speech. In one of them, the lesion was not circumscribed within the left inferior frontal convolution, but spread over the superior temporal and the supra-marginal gyri as well. In the other, there was no definite lesion as such, but rather, a general wasting, affecting in particular the second frontal convolution on the left. To Marie, at this time, there was only one true type of aphasia, that described by Wernicke. Broca's aphasia was a symptom complex, including sensory elements and defective ability to perform the movements necessary for external verbalization. This latter condition, which he called "anarthria," is found in uncomplicated form in lesions affecting the Island of Reil and the contiguous corpus striatum of either the left or the right hemisphere.

This is indeed a meagre review, but it sketches on a flat background the historical relief, against which recent presentations are projected. Further, it demonstrates in a small way the primary importance which methods of observation and theoretical concepts of the general problem have for the analysis of the processes which precede the communication of the comprehension of situations and their interrelationships.

In their recent consideration of the aphasias of the war Marie et Foix (1917) have been uninfluenced either by Jackson or by von Monakow.

The old phraseology is used and no attempt is made to penetrate the processes which lie behind symptom formation. They found two zones of distinctive injury,—an anterior, which gives anarthria and a posterior, which results in aphasia proper. Between these lies a mixed zone. The former comprises the inferior part of the ascending frontal convolution, the posterior extremity of the second and the third frontal convolutions. The region for aphasia itself is bounded anteriorly by a line from the central fissure projected across the lateral fissure; posteriorly, by the cuneus; below, by the outer inferior border of the hemisphere; and above, by the interparietal furrow.

In the anarthria syndrome, after a time during which speech is impossible, a period of recovery follows. The more anterior the lesion in the third frontal convolution, the more complete is the recovery. In the more posterior lesions, the phase of recovery ends in dysarthria, with some slight aphasic symptoms also. Besides, in deep lesions of the anterior frontal region, there is slowness and caution in speech, together with slowness of ideation.

Marie and Foix have separated sensory, or true, aphasia, into three separate syndromes,—that of the regio temporalis, that of the gyrus supra-marginalis and that of the gyrus angularis. Lesions of the foot of the ascending parietal convolution and of the superior temporal gyrus combine the difficulties of anarthria and of sensory aphasia—aphasia globale. In lesions of the temporal region, anarthria is practically absent; comprehension of speech, reading, writing, calculation are about equally affected; there is no hemiplegia; hemianopsia is frequent, but of the typical quadrant kind; intelligence is changed. What we would like to know is the extent and direction of that change in intelligence, and the exact character of the loss in speech, reading, etc. In lesions of the gyrus supra-marginalis, all the elements of speech are almost proportionally impaired, and in some instances anarthria is present. Besides the characteristics of aphasia, there are others:—slight monoplegia of the brachial type; hemianesthesia of the upper limb; no hemianopsia, and sometimes a bilateral apraxia, grosser on the right. Injuries to the gyrus angularis and its nearby regions show predominantly alexia, although writing is preserved. Both the comprehension of speech and calculation are affected, together with the ability to name objects—a characteristic defect which generally appears as a lesion encroaches on the lateral surface of the occipital lobe. Sometimes a slight anarthria is present. As would be expected, hemianopsia is found, hemiplegia and hemianesthesia are not.

It is evident that, in the ten years elapsing between his two papers, Marie had not come to consider "motor" aphasia as a true aphasia, although he admits that in some instances there are slight changes. Yet he does find in "true" aphasias, difficulties in external speech. He has not contributed an analysis of speech, but his careful localization of symptoms is a point of departure for the discussion of the work of Head and Goldstein.

To Head (1923, 1926), aphasia or difficulties with speech and kindred disorders, include all conditions in which symbolic formulation and expression are disturbed. Images, as such, are not affected, but rather a certain use of images. All mental activity which demands symbolic formulation, whether or not exteriorized in speech, tends to be defective. The higher its proportional value, and the more abstract it is, the greater the difficulty. Consequently, the methods devised to study the condition must be carefully considered to bring out various levels of destruction.

Head first allows the patient to match objects, by sight or by feeling, at command. All commands are graded as simple, choice, or complex. Choice and complex commands are always carried out with difficulty, but with a distinctive difficulty in each case. Ability to initate movements, in the looking-glass and face to face, is next tested, followed by the request to translate the movements into words. If the patient cannot call upon the correct words, he is helped, either orally or in writing. The words supplied are classified as those for familiar objects and those for familiar abstract qualities, such as color. The alphabet and the days of the week are used in the same kind of test, i.e , repeating, writing to dictation, saying spontaneously or putting in order. The simple arithmetical signs are used to test the patient's comprehension of a number of relationships. A clock had to be set like another, and, at oral command, at 3:40 or at twenty minutes to four. Oftentimes the last two were not recognized as the same, or one clock might be set like another but all idea of time be gone except its significant relation to the daily routine. Thus 12 o'clock might not be known as twelve o'clock, but, rather, as "when you eat."

The ability to copy printed matter in print, peculiarly enough, suffers in the same direction as verbalization. And the ability to copy printed matter in a cursive handwriting or to write spontaneously is even more affected. Head thinks that copying is a form of self dictation.

Though the patient may be able to comprehend and even to say words he may not be able to formulate. Thus he points to one or two,

instead of speaking, when answering to the compass test. He may be able to choose familiar objects but not to relate them to each other. "The window is there," "the fireplace there." It is easier for him to know that two sixpences make a shilling than the reverse. This sort of study does not allow the classification of aphasia as "motor" or "sensory," nor yet the application of such words as alexia or agraphia. And the result of this analysis of the material, although similar, is differentiated from that of other work by the method of observation and the theory of formulation of symbolic relationships. It is that little difference which is so enormous.

Head has found it possible, first, to group difficulties, and then, to uncover a gross correspondence in the region of cortical loss. In the first group he describes, the most pronounced damage was found in verbal defects. An example (no. 6) will make this clear. At first the wounded man was speechless; later the power of finding words returned in part. He could understand what was said to him. A command exacting a single choice was carried out correctly, but the response to the combination of two orders was slow and hesitating. Simple phrases were badly written from dictation, but he could copy print in cursive handwriting. Later (5 mo.), although he never used the wrong words and his power of naming returned, there was still great difficulty in verbalization. He had no abnormal neurological signs except a transitory weakness of the right half of the lower part of the face and some deviation of the tongue to the right.

Another man (no. 17), a year after he was wounded, was unable to say the alphabet correctly and had difficulty in counting. He checked his own bank book, said 28 for 41, but used 41 correctly. He could do the sum correctly but got the figures wrong. His articulation in reading was the same as in speaking. He could carry out complex printed commands correctly. In reading, he could understand isolated sentences, but could not get all the words, and this lack of words confused him so that he would have to return and read again. His spelling resembled his pronunciation,—manager was said man-ger and so written; pyramid was written either "pyramred'. or "pymerad." The physical signs in the nervous system were gross: spastic hemiplegia; isolated movements of hand impossible; tongue protruded to the right; gross sensory changes of cerebral type; and deep reflexes exaggerated.

The first man (no. 6) suffered from a cut 5 centimeters in length across the posterior face of the inferior frontal convolution. The second (no.

17) had a deep triangularly shaped injury crossing the pre- and post-central gyri, in the region of the lower third of the central fissure.

In syntactical defects, the second group of difficulties considered, there is no want of words, but their combination is so poor that they sound like jargon. In one such case (no. 15), the wrong words were never used but both the rhythm of speaking and the syntax were defective. The patient attempted to rush his phrases, leaving out prepositions, conjunctions and articles, and became confused by his own flow of speech. He understood what was said unless he had to repeat it to himself. He had no difficulty with arithmetical problems; none with the names and relative value of coins. He drew well from memory or from a model and understood the significance of a picture, but he could not explain this in words. This man was wounded by a rifle bullet which entered to the left of the inner canthus of the right eye, destroying it, and emerged directly above the left ear. The only abnormal sign which persisted was a right upper quadrantic hemianopsia.

Another injury (no. 14, in the superior temporal gyrus) belonging to this group is peculiarly illustrative of losses and retentions of abilities of a highly complicated order. The patient could not repeat a sentence, could not find common names, but always chose objects correctly to printed commands. He could not read aloud the commands of "the hand, to eye, to ear" test but could execute the movements. Single words were easily written, but not phrases. He understood French; played the piano; his spontaneous thought was rapid and correct. His intelligence was of a high order but his defects of internal speech hampered its adequate expression.

The loss of names (Head's nominal aphasia) occurred when the area of transition between the parietal and occipital lobe was damaged. A young staff officer (no. 2) suffered an enormous loss of brain substance to the depth of three inches over the angular, superior parietal and parieto-occipital gyri of the left hemisphere. He had right hemianopsia to movement, form and color. Six months after the injury, he could not name common objects and colors, nor use such names in ordinary conversation. He had great difficulty with up, down, to, from, and to, past. But the words which he did use were well pronounced, with normal intonation. And, peculiarly, he was able to explain his inability in an interesting and intelligent manner. He knew differences in color and their significance, although the name was gone. He could not do "the hand, to eye, to ear" test, nor set the clock by a command in words on paper. He could, however, set the clock to a time given in

numbers, and he knew relative values of coins but could not express them. He possessed strong visual images and his orientation was not affected, yet he was unable to draw a ground plan. He could not give a written account of what he had read although he could act out the scene, with appropriate gestures and postures.

In a case of superficial injury to the left parietal region in the vicinity of the supramarginal gyrus (no. 10), the wounded man had no difficulty in expressing by words his ordinary needs, but often, in a general conversation, he appeared to have lost the connection between what he had said and what he wished to say. Nevertheless, all his phrases were perfectly formed and spaced, with correct rhythm and pronunciation. He read aloud correctly and understood the significance of printed words and of short sentences, if they did not contain a command. He wrote very rapidly, as if he feared to lose the idea. He counted perfectly and could name coins but could not solve the simplest problem in arithmetic, and he had been an accountant. He was unable to draw, either from memory or from a model, or to sum in any manner the relative position of objects in a familiar room. And yet he could point to all the objects in the room with his eyes closed, or to them on a ground plan, which, then, with help, he was able to reproduce. He could not find his way about, nor recognize familiar streets. He did not know his right or his left. He was unable to play games because he could not foresee the consequence of the next act. Such an inability to retain either the significance of a symbolic representation in words or pictures or that of an act he was about to do, Head called a semantic defect.

In looking back over these four forms of difficulty with symbolizations, it is easily seen that there is no single instance when a disturbance of one of the phases of verbalization,—speech, reading, writing and the use of numbers,—appeared isolated. All were affected, but to different degrees and in various directions. Activity which demands greater voluntary effort or carries higher propositional value, suffers more, for it has been more lately acquired. It is not surprising, then, to find a certain tendency for the recently acquired performances of writing, computation or the use of money to be disturbed as a whole in a large group of cerebral injuries. But when the observer forced these performances to express meaning or to be mobilized as an external manifestation of a thinking process, they showed themselves to be damaged in ways that are capable of a mobile classification, such as given by Head.

Many of Head's patients said they could "see it in their mind" but they could not make use, that is, express the content, whatever it was,

diagrammatically or in words. In nominal aphasia, the recall of images by words or phrases is uncertain or fluctuating, while in semantic, the details are quite perfect in themselves, but the total is not synthesized. Not a few of these men possessed some knowledge of music. Given the first few notes, they could sing a tune through if the words were not attempted. For example, no. 7, who had been on the music hall stage, suffered from nominal aphasia; without words, the time, the tune and the modulation were correct. The same was true of no. 22, who had lost the power of reading, not only words but also music. In an instance of syntactical aphasia (no. 14) the power of playing the piano and comprehending musical notation was undisturbed, although there was some clumsiness in the reaction of the left hand due to the injury.

Again, it is evident from the illustrative cases, that in the disorders which these patients show, general intelligence is not primarily affected. Rather it is, that general intelligence suffers as a result of the handicap of the individual in his attempt to express his thoughts or formulate his ideas. And unless he improves with time he will become shut up within himself. Moreover, failure and disappointment or an emotional upset may produce a lack of desire to attempt the test, so that he appears more stupid than he is, and may refuse to perform even that which he can do. As in other lesions of the cortex, fatigue and discouragement are important factors in delaying recovery.

Head's latest work (1926) is of interest not only to clinicians, but also to all interested in the processes of learning. The disintegrations have revealed some of the elementary parts. This work lends a new significance to the naming of an object or a relationship; it outlines the necessity for concrete example of principle; for the simple uncomplicated statement; and for the presentation, finally, of material already integrated.

The presentation of this subject by Goldstein (1927) differs, in some respects, from that by Head, but none the less, these men are more in sympathy in their points of view than either with Marie.

In the study of the phenomena characteristic of aphasia, Goldstein thinks that the observer should record not only what the patient can and can not do but also the process by which he arrives at either his right or wrong externalization; for he might come upon the former by a route other than the one he used before his injury. Thus much that has been thought of as restitution is, in reality, only the attaining of the old familiar end in a new and often roundabout manner. Restitu-

tion is, then, not fundamentally a return of function. And a return of function is rather a restitution of the injured substrate, possibly in the passage of diachisis, and can happen, so the reviewer takes it, only in negligible injuries. Further, Goldstein finds it possible to look at any change in the activity of the central nervous system as analogous to the modification of reflexes by cortical or other lesion.

Within each area of lesion, the fundamental function of the brain is injured, which Goldstein designates as "figure background effects." Each lesion allows however a further differentiation of the formation of the disorder. Thus, it is possible to damage regional fundamental activity in high or low degree, and, at the same time, to produce rather widespread associated disturbances. Moreover, significance for symptom formation is allocated sometimes to all areas alike, sometimes particularly to one or the other.

Theoretically it should be possible to differentiate between motor and sensory aphasia, but actually, a pure motor aphasia, with inner speech intact, does not occur. Rather, Goldstein differentiates three manners of using speech. Speech may be employed as a means of representation, i.e., voluntary speech, Jackson's intellectual speech. It is this which suffers most in cortical injury. Speech may be a part of emotional expression, the emotional speech of Jackson. This remains unaffected in cortical lesions; it is more primitive. And, lastly, there is what Goldstein calls common speech, which contains, interwoven, elements both of emotion and of representation. Such can hardly be said to follow willed intention but flows easily, automatically, out of the total psychic situation. It stands intermediate between the other two both in the matter of difficulty of physiological performance and in severity of disturbance in cortical lesions. For its prompt flow, the intactness of the "real" speech center is presumed.

Goldstein's "motor" aphasic can often count, or say the alphabet, but finds greater difficulty with the days of the week or the months because they are less easy to say. He can produce, rather well, something said in rhythm and in series, but the single word in the latter will be incomplete. He seeks an answer to a question out of a repetition of words learned in serial form, in the way that a foreigner learns to pick out the correct verb form by saying a conjugation. Difficult words are always badly spoken. He can speak and read customary phrases, but not the single words of which they are composed. When he reads, he skips the small words such as in, der, op, auf, unten, an, ober, etc. Only with the greatest difficulty can he read, write or speak them.

Such a patient may know a word but not the letters of which it is composed. When a phrase or a short sentence can be said it tends to perseverate. Whether or not a certain word can be written, depends not so much on the type of lesion as upon the individuality of the wounded.

In the next condition which Goldstein considers, motor disorder is a part of a general disturbance. Pure automatic spontaneous words can be seen on the patient's lips, but he speaks little spontaneously. All serial modes of speaking and rhythm are destroyed. He talks in a "telegram style," using only the most important words, and these are not well pronounced. And writing is generally more altered than speaking. He does not know the difference between oben and unten. He can hardly count and has no knowledge of number relationships. He cannot analyze nor understand anything abstract. He must deal with concrete situations. Although such patients are peculiarly aware of the observer they do not notice what another person does. When they do speak it is involuntarily and automatically and without any need on the patient's part to understand.

Goldstein's "central aphasia" combines some of the symptoms of Broca's and Wernicke's description with a disturbance of internal speech, paraphasia. There are two varieties, the "litteral" and the "verbal." In the first the meaning of single words and letters are gotten wrong. Letters may be wrongly placed in well understood words. Such a patient writes as a normal individual would if he had the same acoustic and optic images. The defect is expressive not of destruction of function as such but, rather, of incomplete normal performance. The form of such difficulty is, again, dependent less on the severity of the functional disorder than on the aspects of speech activity which concerned the individual normally. Thus in the diseased condition his individual peculiarities become more apparent. In the second variety, the verbal, there is an alteration of form rhythm. Beginnings or ends of words, and, in writing, capitals are not right. This difficulty of speech is more or less a modification of the normal flow.

Goldstein thinks that these disorders have nothing to do with destruction of symbolic thinking as such. They are changes in the flow of thought, and must be distinguished, above all things, from the destruction of symbolic expression. For, rather, they are directed by a vivid relation between thinking and speaking.

The distinction Goldstein is at so much pains to make does not appear to the reviewer to be as great as Goldstein apparently feels it. If he has been understood correctly, the patient's observed capacity for per-

formance was closely related to the residuum of his thinking processes. When the meaning or significance of particular symbols is lost, the individual falls back upon the symbols remaining—and these he uses, whatever his injury be. What is left must be expressive of the thinking processes present. Head could not be clearer on that, than when he points out that verbal and writing mistakes are commonly the same as those made in thought. Yet Head showed very clearly that the thinking process may exceed apparent expression. Thus, due to the loss of this one type of expression, a patient (no. 2) could not retail the Carpentier-Becket championship fight to the observer in words, but if allowed to act it out, the idea he had of it could be communicated. He had lost only one form of expression, but the one which is considered par excellence, symbolic. On the other hand, Head gives many instances where the individual could express concepts which he had. There is certainly not an exact parallelism between thought and speech. Yet Goldstein says that there is naturally nothing to say of parallelism between the two! Goldstein is not looking at language as a slow growth, built up over long periods of time, expressing in many forms of symbol, relationships in space and time and number. Head uses the word, symbol, in its broadest meaning, a certain class only, standing as names for objects, as names for their relationships, as names for what they can do, or for their qualities.

In discussing the telegram style of disorder, Goldstein thinks that good understanding is possible, only the omission of small conditioning words results in speech which is different from the normal. But these small words are not read aloud and their meaning is not understood. The telegram style is the one which all beginners in the study of a new language use. The dictionary meaning of prepositions and conjunctions may be known, but their significance is not sensed until the language is better understood, that is, until it is "felt." If, in listening to a foreign language, one or two of these little words are lost, the whole idea is gone, although the meaning of every other word can be recognized quickly. In this instance there is no loss in the understanding of the primitive symbols, but rather, inability to relate them. Although an aphasic might not be able to use the words or understand them when read, he might still have the concept of "upon" or "under the table," as distinct from the words as such. Head's interpretation allows the existence of the concept of the relation of the legs to the table independently of the use of the word "under." Goldstein's theory does not. At least, so the reviewer understands it.

There is, throughout these three recent papers, a certain agreement on the localization of the lesions which result in damages to spoken and written language. The lesion for "central" as opposed to motor aphasia, Goldstein believes must lie on the inner half of a region which includes the Island of Reil and the nearby portions of the lobus temporalis, the outer half of the "word blindness" area, and the neighboring parts of the parietal lobe. But there is, nevertheless, a strip of tissue, in the left hemisphere for right handed individuals, stretching from the posterior part of the inferior frontal gyrus across the lower part of the ascending frontal, along the superior and middle temporal convolutions, and over the supramarginal and angular gyri to the superior parietal lobule and the parieto-occipital gyri, which must be intact for the individual to retain all the normal faculties for language formulation and for the understanding of complex inter-relationships. These contributions have not been to the localization of aphasic troubles, but rather to their analysis. Incidentally they have allowed a glimpse into the learning process.

THE FRONTAL LOBE. The frontal lobe, bounded posteriorly by the sulcus centralis (the fissure of Rolando), includes in man very nearly the anterior third of the cortex. The electrically excitable area on the precentral gyrus, and the posterior third of the inferior frontal convolution (Broca's area, field 44) are usually considered separately, yet even then the greater bulk of the enormous subdivision remains. Lying immediately anterior to the precentral convolution is an area (field 6 of Brodmann) of characteristic cyto-architecture, the premotor cortex. This bears a close functional relationship to its posterior neighbor, for certainly it is capable of "facilitating" the activity of the motor cortex and, under certain experimental conditions, itself gives definite movements of the extremities on stimulation. There is, besides, a small area in the center of the second frontal convolution (field 46 of Brodmann; FD_{Δ} of Economo and Koskinas) where electrical stimulation in apes (Leyton and Sherrington) and in man (Foerster) is productive, here of conjugate movements of the eyes to the opposite side. The large remainder of the lateral and medial surfaces of the frontal lobe is "silent." This is the prefrontal area.

To establish the homology of the frontal region below primates is difficult. Kappers (1921) thinks that the two fissures, coronalis and ansata, of subprimates and of Prosimiae, are homologous with the sulcus centralis of primates. With such a posterior boundary the total amount and the proportion of cortical tissue assigned to the lobus frontalis are

less in anthropoid and subprimate brains than in that of man. Brodmann (1912) has given the following figures of the regio frontalis' percentage of the total cortex: man, 29.0; chimpanzee, 16.9; gibbon, 11.0; macaque, 8.3; dog, 6.9; cat, 3.4.

The motor cortex cannot be separated from the area prefrontalis by examination of the surface of the brain; only by faradic current or the study of cyto-architecture. Yet if the motor cortex (field 4) is subtracted, the relative and actual amount of remaining prefrontal cortex is strikingly less for all brains studied among the subprimates and primates compared with that of man. Even in the chimpanzee (Brodmann), the third frontal convolution belongs cyto-architecturally to the precentral motor cortex rather than to the "subregio frontalis inferior" as in man. Yet in all animals so far studied a prefrontal area can be distinguished cytologically from motor cortex by the absence of large Betz cells from the fifth layer and the presence of a distinguishable layer granularis (IV). Considering the phylogenetic antiquity of this and its comparatively recent morphological prominence, it is no wonder that the effect of injury to the premotor cortex should vary as it does from animal to animal and to man.

The cytological characteristics of the prefrontal area are, in man, a continuous inner granular layer (IV) and a thin line of the same type of cell in the second lamina. The inner granular layer (IV) is however not as prominent a feature of this cortex as it is of those parts closely related to the thalamus, the projection areas of the parietal, occipital and temporal lobe. Moreover, this layer (IV) is distinguished, in the frontal lobe, by the additional presence of small pyramids and polymorphous cells. The adjacent third layer of this cortex is poorer in cells than in the posterior lobes. Its sixth is thin. The fifth layer, rich in cells towards the fourth, shows progressively fewer cells as the sixth is approached. By variations on the general cyto-architectural scheme just outlined, Brodmann has identified some eight regions on the lateral surface of the prefrontal areas. Over the same extent Economo and Koskinas found a similar number, with slight modification of boundaries, and they added three more on the frontal portion of the buried cortex. Five of the lateral areas extend over the ridge of frontal area onto its medial surface, where Brodmann has distinguished some seven additional, three of which, certainly, are related to the olfactory system. At the present, however, excepting for the area for eye movements in the second frontal convolution, there are no data for a correlation be-

tween morphological differentiation and function within the prefrontal region.

The frontal lobe is related to the lateral nucleus of the thalamus in Macacus rhesus (Sachs, 1909) by many thalamo-cortical fibers. Those which come from the most anterior part of that nucleus end in the gyrus frontalis superior. From the ventral division of the lateral nucleus, fibers ascend to the "motor" cortex and the postcentral gyrus; those going to the lower limb area arise from the more dorsal part; those for the upper limb and face, and also some for the lower limb, in the middle; while the lowest division sends fibers only to the operculum and facial center. Sachs traced cortico-thalamic tracts, from the precentral gyrus in the macaque and from the "motor" cortex in the cat, ending in the nucleus lateralis and the nucleus ventralis of the thalamus. And furthermore, the cortical excito-motor area for conjugate deviation of the head and eyes may be associated with the colliculi by pallio-tectal fibers. von Monakow (1895) has found, by experimental ablations, that the sigmoid gyri around the fissura cruciatus of the dog, from which Hitzig and Fritsch (1870) obtained reactions of limited groups of muscles, are connected with both the ventral and the lateral nuclei of the thalamus and that the gyrus proreus is related to portion a of the medial nucleus.

Later, von Monakow (1909) studied, in man, the relation of lesions in the frontal lobe to the subcortical regions. With primary lesions in the second and third frontal convolutions, secondary degenerations are seen in the anterior part of the internal capsule and in the medial part of the cerebral peduncle, as well as in the nuclei anterior, medialis (b) and ventralis anterior of the thalamus, the regio-subthalamica and the anterior third (i.e., the medio-dorsal grey zone) of the nucleus ruber. Lesions in the central gyrus of the operculum produce changes only in the nucleus ruber; those in the paracentral lobule in the frontal boundary of the nucleus ruber. Lesions behind the central fissure make no defect in this nucleus.

Dejerine (1901, p. 60) has described a large bundle of fibers which leave the frontal lobe and the frontal or Rolandic operculum and go, via the anterior division of the internal capsule, in part to the anterior boundary of the lateral thalamic nucleus and to the anterior nucleus. Another part passes by way of the medial division of the cerebral peduncle, to end in the substantia nigra or to be continued in the tractus cortico-bulbaris. Dejerine considers that these latter may contribute even to the cortico-spinal system, but the lesion, as shown in his pictures,

included also a part of the inferior end of the ascending frontal convolution.

Certainly, following ablation of the prefrontal cortex in animals, there is degeneration of the medial portion of the cerebral peduncles (cat, Winkler and Potter, 1914; monkey, Ferrier and Turner, 1898). Flechsig (1876) demonstrated that in the development of man the fibers which occupy the anterior part of the internal capsule and end in the pons, myelinate after the cortico-spinal tracts and arise immediately anterior to them. This intermediate region, the premotor, Campbell (1905) believes to be the origin of the frontal-pontine system.

Apparently the non-motor cortex of the frontal lobe is connected by thalamo-cortical systems with the nucleus medialis of the thalamus. Cortici-fugal tracts relate it with the anterior nucleus (possibly the medial in some animals) and the lateral nucleus of the thalamus; with the subthalamus, the substantia nigra, the nucleus ruber and the nuclei of the pons. And, perhaps, some fibers are to be found in the pyramidal system proper. The majority of these subcortical connections constitute efferent systems, hence this region appears, at the present stage of investigation, to be largely dependent for incoming stimuli upon the other lobes of the brain with which it is connected by enormous bands of fibers.

In earlier experimental ablations no sharp line was drawn separating the motor and prefrontal regions of the cortex; in fact no definite boundary was respected as separating even the parietal and frontal lobes. Goltz reported bilateral removal of the anterior part of the cortex of dogs from which sensory disturbances, especially of muscle sense, were prominent. Besides lacking "voluntary inhibition" of cutaneous reflexes, he described that the animals, which had been docile and affectionate, became ill tempered and difficult to manage and very restless. Such an experiment is useless to the modern student, but it illustrates the sort of work which was prevalent in the eighties and nineties when the frontal lobe was thought by some to be the seat of intelligence. But Ferrier's earlier description (1876) of the loss of both frontal lobes in monkeys is worthy of consideration, especially since the appearance of the work of Goldstein and Feuchtwanger. Ferrier reported a decided alteration of the animal's behavior. Instead of taking a curious and active interest in its immediate surroundings, it became apathetic and responded only to the stimuli of the moment or wandered restlessly about. Later, Ferrier (1890) sought the explanation of such results in another direction. He removed the whole of the left frontal region in a

macaque, sparing the motor cortex. The right eyelid drooped and the right pupil was smaller than the left. For the ten days that the animal lived the conjugate deviation of the eyes to the left persisted, but that of the head gradually diminished. All types of sensibility were intact. In this report Ferrier relates the form of mental degradation with loss of attention, which he believes to be "intimately" related to the "volitional" movements of the eyes and the head.

Bianchi's (1922) recent publication shows no such interesting shift in emphasis, but it does give, in no indistinct manner, an outline of the controversy which has occupied this field. His summary (p. 250) would contain more valuable data, if it were possible to analyze the extent of his lesions or the components of certain of his observations. The subject, monkey or man, is torpid, slow in movement, indifferent to persons and objects, easily frightened. There is absence of so-called "choice" and a loss of initiative. Attention is weak and association poor. The "mental" defect is, he thinks, proportional to the extent of the lesion if this is bilateral. And contrary to Munk (1890) he finds no changes in sensibility or movement.

Köhler (1921) has observed that after removal of the frontal lobe, a kind of training which is lost in the dog is retained by the chimpanzee and that there is great improbability that "association" and "intelligence" suffer. It is not impossible that the loss of training in the dog could be laid to difficulties with posture such as described for the cat by Langworthy (1928). Here ablation of the area prefrontalis (the motor area was delimited electrically and histologically and preserved) produces abnormal and enduring (3 months) extensor hypertonus in the heterolateral legs. Langworthy believes that this hypertonus is caused by the release of lower centers from normal control, because when the "motor" cortex is also cut away, no extensor hypertonus is observed. When both prefrontal areas are removed, all four legs are stiff and hyperextended so that it is difficult for the cat to sit or lie down. All postural adjustments are made with difficulty, so that when the animal is placed in an abnormal position, he makes no attempt to escape, and he is unable to jump off or upon a slight elevation. The knee jerks are hyperactive. A crossed extension reflex can be elicited, but flexion only follows maximal stimulation of the footpads, the increase of the threshold of sensibility being explained by the need to overcome the extensor hypertonus. Langworthy's work is so out of line with older reports upon removal of the prefrontal area in monkeys that it calls for

a repetition of the latter—especially now that the central control of posture and movement is better understood.

Midway between the older and newer aspects of studies of the frontal region lies the work of Franz (1907). This investigator removed what he thought were the frontal lobes of cats and various portions of the same areas in the macaque in order to study the relation of these to habit formation and habit retention. When both frontal lobes are destroyed, recently formed habits are lost, those of long standing retained. The former, however, may be relearned. Unilateral lesion of the frontal region is not followed by loss of a habit formed, but there is a retardation of the motor response. The "emotional" condition of the animal remains unchanged. It is difficult to understand how Franz missed seeing aspects of the clear-cut results of Langworthy or results of one-sided lesions given in Ferrier's later paper. The relative amount of cortical loss was less, however, in Franz's experiments on monkeys, and in those on cats he may not have removed the prefrontal area alone. On the other hand, he did observe emaciation and liability to disease greater in the cats than in the monkeys, and a slowing of movement. The latter, being a more drastic symptom in the cat (Langworthy) might make for difficulty in feeding which could be related to their poor survival. Nevertheless why was a new habit lost and an old habit retained? Is it not possible that the regional loss of tissue as such was inconsequential, and that "diachisis," the result of the operation, was the real disturbing factor? The ability of the animal to relearn the lost habits might bear on this question.

An examination of the older literature on lesions of the frontal lobe in man yields discordant results, all the way from no change to very severe alteration of "intelligence" and "character." McDonald (1913) reported that 12 out of 40 idiots showed marked atrophy of the frontal lobe. Bolton (1910) recorded in his study of dementia, as of frequent occurrence, localized wasting of the frontal area. Tumors of the region have given severe psychic disturbances (Oppenheim, 1902; Bruns, 1908; Nothnagel, 1879). In 775 instances of tumor Schuster (1902) counted three times as great a frequency of psychic changes in those of this area as in lesions of other regions. Pfeifer (1910) noted not only intellectual but "moral" changes most often in injuries to the frontal lobe, especially if these were large and bilateral. Others have added to the picture severe numbness, loss of attention and memory, apathy, poverty of movement and want of spontaneity (Bianchi, 1922). Dandy (1925) removed a large part of the left frontal lobe without any appreciable

change; no aphasia and no motor impairment resulted. Others have reported that the initial intellectual damage is later repaired. Jones (1907) found, in one instance of great loss at the anterior pole, normal sensation and movement, but such a grave character change that it was found socially wise to place the patient in an asylum.

It is a relief to read the recent studies because they contain data which a physiologically trained individual can understand. Apparently, no study of injury to the prefrontal area has emerged from wounds to English soldiers (although Holmes (1927) says that he has seen many), and but few in France compared to the numbers reported by German investigators. Marie and Béhague (1919) describe, as changes in intelligence, a kind of torpor, slowness in the execution of acts or the formulation of ideas and sometimes marked irritability. With deep lesions they observed gross disorientation; the patient loses himself in a familiar room such as his hospital ward; he knows none of the streets in the vicinity of his home; and not even his left hand from his right. In less severe injuries he cannot tell to which side he has been rotated. He often has trouble with time. On the other hand, there is no disturbance in the order of words, or in their use; no loss of memory. Muscular force, sensibility and reflexes may be normal (ob. VI) and orientation all right except when the eyes are closed, but following the rotation test all the responses may be erroneous.

Five years later, Marie together with Bouthier and van Bogaert reported a slow growing tumor in the right prefrontal region in which the dominant symptom was disorientation in space. There was no change in sensation, none in movement, nor in the reflexes studied. The patient was a violinist; after he had been escorted to the door of the theatre he would lose himself on his way to the pit. Another type of change was noticed: he talked of subjects which are socially taboo in France,—a symptom which gradually regressed after removal of the tumor.

These modern studies have, then, contributed a new symptom, spacial disorientation. Further, in his discussion of cerebellar injuries Andre Thomas (1918) distinguishes a cerebellar ataxia from a frontal ataxia. In the beginning, cerebellar ataxia shows no modification of reflexes, of muscular sense or of voluntary movement; frontal ataxia shows no adiadochokinesis, no asynergia, no dysmetria and no scanning speech. On the contrary, Goldstein (1923) finds certain similarities in frontal and cerebellar lesions, namely, adiadochokinesis, prolongation of motor reaction time and a disturbance of evaluation of weight and size.

He noted a certain correlation of site of the injury and distribution of motor disturbance. Lesions in the midfrontal region give disturbance of eye movements; those at the foot of the first convolution, disturbance of head movements; and those of the medial and basal parts, ataxia of trunk or body musculature.

These localizations correspond loosely with the observations of others. Bartels (1919) described a center for eye movements in the middle of Brodmann's field 6, an area slightly posterior to Goldstein's and yet coming under the periphery of Foerster's (1926) area for clonic deviation of the eyes to the opposite side. Müller (1902) found side movements of the head resulting from lesions in the lower part of the foot of the second frontal convolution. And Gerstmann (1916) found that ataxia of the trunk could be correlated with injury to the medial and basal parts of the frontal lobe. Such disturbances of coördinated performance are often mixed with true motor paralysis of the precentral type.

Small tumors of the posterior part of the first frontal convolution (premotor of Campbell, field 6 of Brodmann) have recently been associated by Adie and Critchley (1927) with a peculiar disorder—involuntary grasping and groping movements in the limbs on the side opposite the tumor. The fingers close over any object which touches the inner surface of the hand, and when the patient voluntarily attempts to release it, the grasp increases. The extensors are powerfully innervated but the flexors fail to relax. Any light moving stimulus over the volar surface causes the fingers to make a slow movement which is a combination of flexion and extension, appropriate for surrounding an object. At times such a stimulus is followed by rotation of the forearm, after which the arm and hand may move in the direction of the stimulus very like a man in the dark groping for an object which he thinks to be there. This reflex closure also occurs when the patient is handling objects voluntarily.

Whenever forced grasping is present, Mayer's reflex is also exaggerated; that is, the thumb is adducted by a forced flexion of the proximal phalanx of a finger upon the palm. The loss of this reflex precedes an oncoming paresis. Forced grasping and groping may be found with the voluntary power of the affected hand intact or when it shows any degree of impairment short of complete paralysis. When paralysis is complete, however, the reflex groping and grasping disappear. Therefore Adie and Critchley believe, with Mayer, that an intact pyramidal

system is essential for the appearance of an exaggerated Mayer's reflex and for the best development of forced grasping and groping.

As "tonic innervation," similar phenomena were described by Wilson and Walshe (1914) as resulting from large lesions involving not only this same area but also the posterior half of the second frontal convolution (tumors the size of a tangerine). The "tonic innervation" is inability voluntarily to relax the innervation of any group of muscles. In two of their patients, the innervation of the muscles of the left arm and in a less degree those of the leg could not be inhibited. The more the patient attempted to relax, the more distinctly the muscles could be seen to contract. This phenomenon was unaccompanied by any change in sensation or by ataxia. In both these patients the left limbs became gradually hemiplegic, without, however, great loss of strength. And as with forced grasping and groping, the difficulty in relaxation of contraction mitigated as the hemiplegia became more complete. After the removal of the tumor, no trace of the tonic innervation was left. These then became typical cases of moderate hemiplegia with characteristic exaggerated reflexes. The conditions just described were present without sign of psychical disorder, without change in sensation, without diminution in voluntary movement and without any alteration in tone.

Phenomena resembling forced grasping and groping, but complicated by other conditions such as sucking (ansaugen) and polymorphous hyperkinesis, have recently been described by Schuster and Pinias (1926) as Zwanggreifen and Nachgreifen. As in Adie and Critchley's report, touching the volar surface of the hand causes the fingers to flex so tightly that relaxation is difficult, but they add that stroking the dorsal side of the fingers results in their extension. These reactions vanish after "motor" aphasia and paralysis are fully developed. The site of lesions, however, was not confined to the frontal lobe. Lacunae and cysts were found in the corpus striatum as well.

The new findings, spatial disorientation, ataxia in coördinated performance, disturbed inhibition of established contraction, although capable of more objective study, have not masked entirely the older great group of symptoms which might be classed largely as psychic disturbances. Both groups of difficulties have been recognized and studied intensively by Feuchtwanger (1923), and treated in a masterful manner by Goldstein (1927).

In Goldstein's observation there is often great disturbance in conjugate deviation of the head and eyes and uncertainty in the use of the

body musculature in sitting, standing or moving. Such difficulties eventually grow less if the injury is unilateral, and reappear only under psychic stress or in a quickly directed movement. Even the ataxia can be controlled. When the body ceases moving, it comes to rest with a forward inclination. With the eyes closed the patient tends to fall toward the side opposite the lesion and pass points in the same direction. The raised arm involuntarily deviates to the side opposite the lesion. With these difficulties others appear. A motor response is wrongly evaluated. The motor reaction time is lengthened. The so-called tonic reflexes are abnormally strong and the opposite labyrinth is over-excitable. Goldstein found, moreover, that this overexcitability affects other organs as well,—skin, eyes, hearing, to such a degree that motor and spacial adjustments are improper. In unilateral frontal lesions the hyperexcitability of the opposite labyrinth contrasts well with that of the cerebellar lesions where the difficulty is on the same side. In bilateral frontal injuries both labyrinths are affected, but it is the opposite one which shows the greater excitability by test. These difficulties were correlated with injury in Brodmann's fields 6, 8 and 9 (Economo and Koskinas; FB, FC and FE).

Bartels (1919) distinguishes nystagmus of cortical origin from that of vestibular by the quicker deviation, slower compensation, and short duration of the former. This nystagmus of frontal lobe origin is difficult to differentiate from changes in the tone of the opposing extrinsic eye muscle amounting in some cases almost to paralysis. If for example the patient has a right deviation paralysis, even a slight turning of the head will produce an extraordinary nystagmus with an intense after nystagmus toward the left. In cases of cortical deviation paralysis and a loss of frontal cortex, the vestibular nystagmus toward the opposite side is greatly increased.

In their study of the relation of visual nystagmus to cerebral lesions, Fox and Holmes (1926) found that in a unilateral injury to the second frontal convolution lateral nystagmus to the side opposite the lesion is destroyed. These observers think that the posterior part of the second frontal convolution is connected by fibers with the occipital lobe, and any injury between the two regions interrupting them, destroys the normal optic nystagmus. This hypothesis is partially supported by Cords (1926) who reports that destruction of the optic motor field (field 19 of Brodmann) or of the optic motor pathway, which underlies the intermediate area outlined by Fox and Holmes, also destroys visual nystagmus.

Feuchtwanger describes disturbances of equilibrium and movement

similar to those reported by Goldstein, and others which resemble the disorders of striatal disease, such as rigidity and propulsion, compulsory crying and laughing. Foerster (1921) has also mentioned, in lesions of parts one and two of the prefrontal lobe, kataleptoid phenomena. The reflexes he described as normal. Schultz (1915), and before him, Grainger-Stewart (1906) reported, to the contrary, a suppression of the abdominal reflexes on the side opposite the lesion. Feuchtwanger found, however, no uniformity; sometimes these reflexes were exaggerated, and sometimes diminished, either on the same or opposite side; sometimes they were normal. Nor was he able to confirm the vasomotor hypoactivity seen by Schultz, although he did observe in different cases a vasomotor disturbance such that the face and feet were chronically blue with an increased tendency to perspire.

Liepmann (1900) observed a certain group of phenomena which he named apraxia. He defined this term as the inability to act or to move any part of the body in a purposeful way, although no paralysis is present and "the individual possesses a sufficient sensori-motor apparatus." Difficulty with the relaxation of contracted muscles is often accompanied by some manifestation of Liepmann's phenomena. Wilson (1908) noted such inability to perform a required act although voluntary control of the muscles was present in cases where the total cortex was normal except for the left frontal area. Such a lesion involved not so much the projection as the association systems of the first and second frontal convolution. A year previously Liepmann and Maas had described a case of right hemiplegia with left agraphia and apraxia of the left upper extremity. At autopsy the right hemisphere was normal. The right hemiplegia could be explained by a lesion in the pons. In the left hemisphere there was a lesion in the first frontal convolution which involved a part of the paracentral lobule and the anterior two-thirds of the corpus callosum on the left. In the same year Rothmann found a similar condition in two left handed patients with left hemiplegia, right apraxia and right agraphia. Schuster (1923) studied three patients (no autopsy) who presented symptoms of forced grasping in the right eupractic hand, apraxia of the left side, and a right sided paresis which had affected the upper extremity to a lesser degree.

Apraxia often touches but one limb only and generally the upper. It is associated commonly with lesions in the left hemisphere, either cortical or subcortical, but never with capsular injuries. It may be crossed or uncrossed. And the question naturally arises,—Is the capacity to use an object or to make a definite requested movement on both

sides of the body unilaterally represented? Rothmann's right sided apraxia in left handed individuals causes one to wonder whether or not eupraxia, like "motor" speech, is not a function of either the left or the right prefrontal cortex alone.

Apraxia, as recently discussed by Goldstein (1927), must be distinguished from motor aphasia. It is rather the impairment of the use of face, tongue, larynx and head musculature and affects, therefore, the performance of speech, writing, singing and mimicry, without, however, any loss in the understanding of requested movement. The patient may understand what he reads, and, although he cannot write with the affected arm, he often can with the other, and he always insists that he knows what should be done. This akinesis (Goldstein) may eventually appear in all performances so that ordinary spontaneity is more or less lacking. It may affect a half of the body or a circumscribed region, or a particular performance. And in the akineses of speaking, the "telegram style," "agrammatismus" appears (Isserlin, 1922). For the body this impairment is generally crossed; in the facial musculature it is often bilateral. The difficulty with speech may be seen in lesions of the left frontal lobe or of both. According to Goldstein, this akinesis may be explained as a primary psychic damage or as damage to a frontal lobe mechanism which supports the working of the basal ganglia. It is possible that the cortex influences the activity of the basal ganglia, not directly, through collaterals from cortici-fugal tracts, but in an indirect manner via cortico-thalamic (to the nucleus anterior) and thalamo-striatal relations (nucleus anterior to nucleus caudatus). Goldstein believes then that the frontal lobe aids the initiation, the flow, and the cessation of voluntary movements perhaps by way of the corpus striatum —a suggestion plausible in the light of certain similarities in symptomatology of injury of this region and of the basal ganglia.

The recent studies of psychic disturbances are marked by emphasis on the ability of the individual for concrete performances. The observers have the attitude of Hughlings Jackson, "What can the patient do?" Yet there are other aspects of the disorder resulting from lesions of the frontal lobe. The patient appears inattentive; he does not observe many things that go on in the vicinity. The time of comprehension is lengthened, but becomes better when the stimulus is repeated within a short space of time. There is difficulty with the reproduction of old material and the acquisition of new. These can be considered as fundamental damage to the comprehension of the outer world. Furthermore, Feuchtwanger's patient, Ra, could move correctly, had

good "intention," made good movements and assumed correct postures, but the determining tendency, the "willful" content was destroyed. There are marked deficiencies and distortions of the emotional life, although no case of disorder of a single affective quality exists. Rather, the patient is unable to appreciate the whole of a given situation; to find the full sense of an emotional occurrence; or perhaps to maintain order in the emotion itself. An old difficulty reappears in the analysis of the frequently observed "character" change, the loss of social and ethical standards. Is this of the same order as the lack of inhibition of movements already noted? Or do the peculiar witticisms so often described grow out of the lack of complete comprehension, the seeing of an isolated part only?

Feuchtwanger has described manifold psychic disturbances under such heads as hypo-maniac ill humor, mania, sexual erethismus, depressive conditions, schizophrenic-like and hysteroid conditions and epileptiform phenomena without aurae. In some cases he found intellectual disturbances only; in others, the individuals were morally and intellectually sound but were psychopathic; and in others there were no effects. The whole of the older literature can offer no greater variety. It is hoped that those who have said that no changes follow frontal lobe injury will hereafter add the phrase, "in their experience." And it is possible that their experience means in reality, an inadequate ability to realize it fully.

Goldstein's summary of the result of frontal lobe injury is worthy of consideration. Static and locomotor disturbances and inability to check a movement, apraxia and akinesis, and, finally, characteristic psychic impairment might be correlated respectively with the frontal lobe's relation to the cerebellum (fronto-ponto-cerebellar tracts) and to the basal ganglia (via fronto-thalamic paths) and with injury to the prefrontal cortex itself. The characteristic over-reaction to stimulation of the vestibular apparatus; the overestimation of form, shape, weight; the lengthening of the motor reaction time, and the ataxia of trunk musculature are peculiarly reminiscent of cerebellar injuries. The mechanisms for conjugate deviation of the eyes and head are closely related, apparently, to subcortical centers, for, as in Sherrington's ablations of the eye deviation center in the chimpanzee, the disturbances are quite transient and reappear later only under stress. Trembling, compulsive crying and weeping, a certain hypertonia, abnormal expressive movements and katalepsy may be the expression of striatal relationships. The lack of inhibition, both psychic and motor, impaired

attention, the abnormal arrest and repetition of reaction, the peculiarly strong affective reactions may in part be thought of as the activity of this tissue in relation to other regions of the cortex.

Apraxia and akinesia in man remind one of the facilitation in experiments of Graham Brown and Sherrington on the premotor region and it is not unthinkable to consider that the voluntary quality of movement, so long thought of as a function of the precentral convolution, is rather a particular attribute of the activity of the prefrontal cortex. Forced grasping and tonic innervation in man are peculiarly reminiscent of the extensor hypertonus in Langworthy's cats which follows removal of the prefrontal cortex and, like the two difficulties in man, disappears upon the establishment of complete paralysis. Although these areas in the cortices of man and of cats are not cyto-architecturally similar, yet their intactness allows in either easy inhibition of voluntary or involuntary contraction of muscles. This condition is not facilitation of movement in the exact sense of Graham Brown and Sherrington; it is facilitation of inhibition and makes the next movement possible.

The disorientation in space of the French authors, and the inability to relate oneself to the whole of a situation, may be but the background out of which grows the individual's ability to orient himself to the social and ethical restraints of his group. The frontal lobe may not be the seat of judgment and intelligence, but it does apparently give the individual a smooth and easy start, aids the consistent flow of movement and life and allows of checking quickly without too much jarring, in the spheres both of phenomena and of neumena. It is improbable that animal experimentation will duplicate these results, but certainly the outlines are indicated; and only through experimentation can the peculiar function of this part of the brain of man be adequately approached.

TASTE AND SMELL. At the close of this discussion of the function of the neopallium, the archipallium and paleopallium merit slight attention. Smell and taste, unimportant as they appear in the active life of man, have not disappeared; but remain, and are capable of rather complicated training. The present position of the smell cortex, inrolled in the posterior part of the lateral ventricle, is ignominious when compared to the relatively generous allotment of tissue on the medial surface of the hemisphere in a macrosmatic animal. And yet the system remains. The hippocampus is thought, upon the basis of its peripheral connections, to be the sensory projection center for smell; the gyrus hippocampus, related to the former by the alveus and the transitional cortex,

the subiculum, is interpreted as an association center for smell; while the uncus is considered to be representative of the old pyriform lobe. The fact that uncinate fits (Mills, 1908) are often preceded by a taste aura, led some investigators to believe that the uncus is a cortical center for taste. Henschen (1900, 1918) thought that taste could not be localized in the hippocampus nor in its vicinity. In some fishes, the pyriform lobe receives an ascending system from the hypothalamus which in turn is connected via the mid-brain with the taste center of the medulla, as well as the lateral olfactory tract. Upon that evidence alone rests the interpretation that besides being an area for olfacto-somatic correlations it is also a center for the correlation of olfactory and other visceral (taste) sensibility. Becterew (1900), on the other hand, has placed a taste center in the operculum of the posterior central gyrus; and recently, upon the basis of lesions, Boernstein (1921) has substantiated him.

A POSSIBLE FUNCTION FOR THE LAYERS OF THE CORTEX CEREBRI. The variation in size and distribution, from animal to animal, of the several lobes of the cerebral hemisphere and the probable relation of function to these have been discussed. At the same time the cellular architecture characterizing different parts of the pallium has been comparatively outlined. But no attempt to relate particular significance to the relative development of particular layers of the cortex has been made.

In the consideration of the phylogenetic development of the cortex, the granular cells of the primitive hippocampus of the amphibian telencephalon were described, after Kappers (1909), as the receptive cells for the incoming olfactory neurones, and the multipolar cells which lie among them as probably giving rise to the fornix and, in part at least, to the commissura pallii. In reptiles, the prevailing receptive neurone for this same cortex is the granular cell of the "fascia dentata" (Meyer, Kappers) which is related by its neurites to the hippocampus in which cells of the pyramidal type predominate. The sub-cortical projection fibers arise in a manner similar to that in the amphibian brain. The hippocampal cortex, in turn, is connected laterally with the general pallium. In the olfactory cortex of the lowliest mammals there is an increase in the number of pyramidal cells, from which the fibers forming true projection systems and bilateral association tracts spring. In the association area a great number of the supragranular pyramids send their dendrites up into the outer molecular layer, thus serving for intraregional connections. Others, the subgranular pyramids, give rise to

bilateral association fibers and to the fornix, inter-regional and projection connections. With such a phylogenetic history behind these most primitive of cortical cells, one would anticipate in the embryological development of a mammal, by way of ontological recapitulation, a certain definite sequence of differentiation.

In Bolton's study of the development of the human cortex, mentioned in the first part of this discussion, early laminar differentiation was described. At birth, or shortly after, the two outer divisions of the granular layer (IV) in the visuo-sensory cortex are almost the thickness of the adult, and the inner (c of IV) has attained but four-fifths of its future depth. The infragranular layers (V and VI) are four-fifths and the supragranular, five-ninths of the thickness of the normal adult. In the visual association area (fields 18 and 19 of Brodmann) the granular layer (IV) is almost complete in its depth but the outer lamina are at birth only two-thirds and the inner lamina, three-fourths of the depth of the adult. These findings are in marked contrast, on the one hand, to those for the sensori-motor region, where the Betz cells of the fifth layer are well developed in an eighteen week embryo and lie in their adult relationships to the growing central fissure, and, on the other, to the prefrontal region, where at birth the outer lamina is one-half, the middle three-fourths, and the inner, almost the thickness of the adult cortex. These various regions develop, then, in the following order: pre- and postcentral cortex; visual projection area; visual association and prefrontal cortices. In the first and the last, the order of laminar development is inner, middle, outer; but in the two areas of the occipital cortex studied the inner and middle were reversed.

In order to test the dependence of cortical layers upon lower centers for their development, Nissl (1911) cut away one-half of the cortex from the thalamus in new-born rabbits, leaving, as far as possible, the blood supply intact. The results were astonishing. The cells in layers two to five constituted strikingly thick laminae, although layer three was deficient. The contents of all laminations tended to vary proportionately, though the greatest differences were found in five and six. In spite of the marked limitation of function, there had been growth in all layers, but, although the inner part of the cortex had differentiated further than the outer at the time of operation, layers five and six grew much less thereafter than the other four. The growth of the outer layers may be inter-dependent and bespeak a certain inter-regional correlation, while the deficiency of the lower two may mean that they

are mainly dependent upon infra-regional relationships, especially with the thalamus.

This type of layer deficiency is further substantiated by Bings' and Winklers' report (see Kappers, 1909) upon differential reduction of lamina in two deaf individuals. Both found the defect confined to the infragranular reaches ($\frac{3}{5}$ of normal). Bolton (1910) reported a long-standing optic atrophy in which the line of Gennari was decreased fifty per cent, and lamina "a" of layer four, ten per cent. There was no change in the supragranular laminations. Kleist (1926), discussing the divergent results of investigators, quotes Cramer as finding, after a long-standing case of right-sided blindness, greater loss in the opposite cortex. The outer granular layer (IVa) suffered more on the right and the inner (IVc) on the left. But besides these losses, there was a marked bilateral reduction in the fifth and sixth layers, more severe on the right. The subgranular layers seem to depend on the intactness of their relation to subcortical systems. They subserve projection, and intra-regional association, and increase phylogenetically after the formation of the granular layers. The supragranular layers seem more dependent upon inter-regional associations. They are last to emerge phylogenetically and remain almost normal after subcortical lesions.

The comparative studies of Watson (1907) and Mott (1907) offer some further evidence for the functional interpretation of cortical lamination. Watson found that the optic cortex of the hedgehog possesses a thin supragranular region, which is practically absent in the almost blind mole and shrew. In his study of the phylogeny of the visual cortex Mott found that the more dependent the animal in question is upon vision the greater the complexity of its visual cortex. The transition from panoramic to stereoscopic vision is attained by increase in the number of uncrossed fibers in the optic neree, which Mott thinks may be correlated with a progressive development in the outer pyramidal lamination (II and III). Carnivorous animals, such as the "cats," whose eyes are directed forward, have many direct fibers in the optic tract, while the caninae, whose eyes are set further apart have fewer. Although the latter depend upon quick correlation of visual and motor mechanisms for seizing their food, the foreleg is not free as it is in the cat. That animal not only can catch rapidly moving objects but also can subject them to a certain amount of examination by turning them about with the free forepaw. The visual-sensory cortex of the dog possesses a receptive layer and an infragranular lamination very similar to that of the rodents and ungulates, whose vision is almost panoramic,

although the supragranular layers (II and III) possess many small and large pyramids. The granular layer itself in this cortex is not well differentiated, yet several types of pyramids may be seen within it. On the other hand, Mott finds that the visual sensory center of the cat has a more highly developed outer layer of pyramids, a more highly differentiated receptive region (IV) and infragranular lamination which is not quite as thick relatively as that of the dog.

In primates convergence of the eyeballs and binocular stereoscopic vision are associated with a forelimb particularly free from serving body support, and with eye movements in all directions independent of head movements. This phylogenetic change in functional relationships may be correlated with rather specific anatomical developments; a definite macula lutea, gradual increase in the number of uncrossed fibers; the appearance of a nucleus of convergence in the midbrain; a line of Gennari, visible to the naked eye. A definite "associational zone" appears; the depth of the supragranular layers increases, and large pyramids are seen in the fourth layer. The latter cells, Mott believes, serve as association neurones between the sight cortex and other parts of the cortex, such as, he says, "auditory and tactile motor areas." Further, he correlates the increase of the outer "associational zone" with the gradual increase of the visual-psychic cortex, and of the parietal lobe.

Looked at for cytological dominance, granular cells prevail in the less developed visual cortices; large pyramidal and polymorphous cells, which constitute the subgranular lamina, become more numerous in the more developed; and when a center for so-called higher visual association is added, the pyramidal cells of the visual cortex itself are greatly augmented and form a thick outer lamination. And the receptive layer itself undergoes marked differentiation until it is seen as a complicated tristriate lamina.

Bolton's (1914) generalization, made from his comparison of the inner and outer lamina of the Betz cell region of the dog, of the macaque and of man, that the increase in actual depth of the supragranular layers is not dependent on increase in muscular bulk but rather on greater educability, is slightly disturbed by Van't Hoog's finding that the depth of this area is much greater in both the adult chimpanzee and gorilla than in man, although, as pointed out previously, the relative excess of thickness of supragranular over infraganular layers in the motor cortex is greater in man. To justify fully his conclusion, Bolton should have compared the thickness of these layers in men differing widely in muscular bulk.

Consider, again, the difference in the permanent defect depending upon the depth of the injury to this cortex. By Head's observation there is, in superficial injuries, loss in two and three dimensional awareness, and in the sense of position and passive movement. The initiation of movement is easy, and there is no hypertonus, and little or no change in reflexes. In deep lesions, such as Horsely's removal of the arm area in a boy, there is loss of muscle sense. Lack of facility and incoördination characterize movement, and a slight, differential distribution of hypertonus and exaggerated tendon reflexes are present. The loss of freedom of movement is not accompanied by exaggeration of associated movements. Certainly there is a marked difference in the results of superficial and deep injuries. If Bolton is anywhere near right, educability may inhere in the upper layers where the interpretation, correlation and discrimination of incoming proprioceptive sensibility seems to take place. It is that loss for which Head's patients, who were not paralyzed, found it difficult to compensate in the execution of coordinated movements.

Bolton's (1914) study of the condition of the cortical layers in amentia and dementia offers some evidence for further interpretation of the function of these layers. Amentia is, by his definition, the mental condition of a patient suffering from deficient neuronic development; dementia, a permanent psychic disability due to neuronic degeneration. Bolton stripped the hemispheres and compared the average weight of the cortex of "lunatics," showing little, moderate and gross wasting, with what he thought to be the normal. Between the extremes of abnormal, of both men and women, there was an actual difference of forty grams; between the least wasting and the normal, for men there was a difference of thirty-seven grams, for women, fifty-three. Since his normal was not an average, but an actual weight, the differences may mean nothing, or may indicate the direction of cortical defect only. The regions which were most affected, given in descending order, were: the prefrontal area; the first and second frontal convolution (apparently Brodmann's field 6); the ascending frontal gyrus, with Broca's area; the superior and inferior parietal lobes, with the first temporal convolution and the insula. Wasting was always less marked in remainder of the cortex. Brouwer (1927) has also noticed this preference of generalized pathological processes for the phylogenetically newer parts of the cortex. He says that "it cannot be expected that the rule, that the younger parts of the nervous system resist noxious agents less, is always clear in pathology. . . . . But it is certain, that, when a

pathologist is acquainted with the relations in comparative anatomy, he sees such analogies more frequently than others do."

But does this process of wasting select specific layers? Bolton examined twelve brains cytologically, selecting three areas for study. Five of the twelve visual association areas were normal. In the remaining seven, lamina five and six most constantly approached the normal; four, the next; and two and three, the least. The same order of change was found in the visuo-sensory area, in five brains. In the prefrontal cortex the severity of the change always varied directly with the degree of amentia or dementia. In imbecility, although all layers may suffer, the greatest difference was seen in the outer two. Examining these brains as grouped by the severity of the individual's functional disability, in the prefrontal cortex of gross amentia, the granular lamina (IV) was approximately one-half its normal thickness, the infragranular (V and VI) approached the normal, while the outer layers were less than one-half their proper depth. In gross dementia, which Bolton considers less severe than the preceding, the receptive layer (IV) was practically normal, five and six might be almost normal, but the outer two suffered a marked diminution in thickness in the number of cells present. Neuroglia were very prominent. Bolton is well aware of the criticism which this work may merit;—first, because of the uncertainty of obtaining strictly comparable areas, and second because of the difficulty of orienting the block of cortex so that the depth is taken in a plane exactly perpendicular to the surface. He attempted, also, to discover an age factor in depth but was unable to do so. Certainly his photographs show very marked changes, and his material justifies serious consideration of his conclusions.

The infragranular layers, which are developed early both phylogenetically and embryologically, are commonly less modified by disease, but in the prefrontal region, which as a whole is new, even these exhibited a lesser defect in amentia and dementia. The granular and infragranular layers in the visual association region approximated the normal in nine out of the twelve brains studied; in the visuo-sensory area these stratifications, with the exception of the outer division of the granular (IVa), approached the normal. The greatest decrease of depth in these two cortices was in the supragranular stratifications. In the prefrontal area both the granular and supragranular levels were definitely subnormal. The supragranular reaches of the three cortices show the greatest differences in evolution. They are the last of all layers to be evolved, and appear first in the visual sensory area (field 17), next in the visual

association (fields 18 and 19 of Brodmann) and last in the frontal lobe. Bolton believes that the cortex is developed from three primary cell lamina: an inner, which is concerned with performance of organic and non-voluntary activities; a middle, which is receptive; and an outer, "the physical basis of the association or psychic functions of the cerebrum." "The associative function of the outer pyramidal lamina may be regarded as 'voluntary associative,' in view of the fact that the essential feature of amentia and dementia is decrease, instability, or loss of voluntary control over the processes of cerebral association." One wonders if a modern student of this material would reach a similar conclusion.

The evidence presented, gathered from phylogenetic, ontogenetic, experimental and pathological studies upon the histology of the various cortical layers and their relative distribution in the hemisphere, seems to indicate that a receptive layer is first established, together with projection cells whose fibers terminate in lower motor centers, both together forming what is known as the sensory projection area. As cells of projection, polymorphous cells are older, later to be outnumbered by pyramidal cells. The projection cells also serve bilateral association. When a definite association center appears, pyramids will be found among the granular cells there. And, as projection and association areas develop further, there is within them an increase both of infra- and of supragranular pyramids, but in particular, of those in the outer lamina (II and III). Further, stratifications are noted within the receptive layer itself; it contains many elements which perform functions other than that of simple reception. The major connections of the infragranular layers are intra-regional or projectional; of the supragranular layers in the main, inter-regional.

Throughout the mammalian series of all the cortical laminae the infragranular layers are most constant. On the other hand, the granular layer may vary markedly not only with the species studied but also in any single individual, from region to region. But the supragranular layers are indeed the most labile, whether studied in the same or different animals.

Therefore we find, generally speaking, the greatest changes following subcortical lesions in the infragranular layers, except for the marked atrophy of the receptive layers of the visual cortex, as well as a reduction in layers V and VI in long-standing blindness. But when the stratifications are studied, in certain general pathological degenerations, the greatest variation from the normal is seen in the outer layers (II and III).

These are the layers of the motor cortex, for example, in which Bolton found great differences in relative depth in his comparative study of that region in the dog, the macaque and man. And these same layers, which he believed were "educatable," are the ones which superficial injury has shown to be not necessary for movement as such, but significantly modifying it. Again, they are the layers in which Bolton described either the greatest failure of development in amentia or the greatest loss of neuronic elements in dementia.

Apparently, there is some relation between peculiarities of development, and neuronic relationships, and pathological involutions, which expresses itself in the individual as little modified control of the activity of the lower strata of the cortex. The so-called instinctive acts were not given uncontrolled freedom of action in any definitely circumscribed lesion of the cortex except in some injuries described for the prefrontal area. And it was this region in which Bolton found such marked changes in what he called normal control over cerebral processes and associations. And if that loss might be interpreted as one of meaning or significance of the totality of an observed situation, it would apply in a rough manner to the loss of function seen in several aspects not only of frontal lobe lesions but also of those in the parietal lobe and certain of them in the occipital pole.

DISCUSSION

The history of the concepts of localization and function within the cerebral cortex is indeed one aspect of that of human thought. The interpretation of observations, and even the observations themselves, have been limited not only by theories of physiology and psychology then prevalent but, also, at certain points, by those of philosophy. This history has passed through an early period, the time of Gall, when definite attributes of character were generously pasted on the lobes. In Goltz's laboratory hemianopsia was found when the locus of will was sought. Then different centers were plotted for various functions, such as reading, writing and intelligence in general. And now, although the first two have been partially analyzed as complex psycho-physiological acts, the last, as the recent reports of prefrontal lesions demonstrate, still remains resistant. In this manner cortical diagrams, so prevalent in the last part of the nineteenth century, gradually became dimmer until finally point localization disappeared even from the motor cortex before the careful analyses of Leyton and Sherrington and Graham Brown. Only the projection of the retina upon the area calcarina now

remains. And yet, in view of the data presented in this paper, to consider the cortex as equipotential is hardly justified, nor to hold the opinion that the kind is immaterial, providing the bulk is sufficient.

Injuries to the cortex do not remove a center for any particular highly organized activity; rather, they disturb complete function in relation to the phase in question. And the activity of the remaining cortical tissue may then be read. But that there is some correlation between the place and depth of the lesion and the type of disturbance of activity which follows, multiple observations make well nigh indisputable. The use of the modification of such simple reflexes as the knee jerk or the Babinski for the diagnosis of lesions of certain descending pathways, is a simple case in point.

Modern clinical investigations are carried out in a manner similar to physiological studies. The clinical observer has become a physiologist in that he recognizes the difference between acute and chronic preparations and has learned to discard, as valueless for analysis, conditions which grow progressively worse. But there is this great difference, a certain amount of conscious coöperation between observer and subject is necessary,—and yet another, the methods used in the first field are standardized; in the second, the method of testing is individual, and will remain so, until the evaluation of changes in activity becomes more important than the necessity to put across the observer's method. But individuality, again, is a characteristic of the activity of the cortex, in that it allows an alteration in sequence or an interpolation. Yet to reach uniformity in examination would be a cortical act itself, calling for an inhibition of the personal variety which many observers enjoy exercising.

Viewed as a whole, the central nervous system is conservative. There is no evidence, at the present, of a loss of parts in evolution; rather, newly differentiated areas and regions are continually superimposed on the older centers and modify their activity by a new demand of discrimination, a diversion of significance.

The interpretation of the function of distinct regions within the telencephalon of lower vertebrates based upon analysis of fiber connections, although it aids the understanding of the parts in question and allows the investigator the delight of creating homologies, is not completely justified. The area striata bears the same relationship to its thalamic center, the lateral geniculate body, as does the postcentral gyrus to the "optic" thalamus. Both are sensory projection areas at the same neuronic level. Yet a study of the type of loss suffered by each cortex

proves them to possess a physiology which differs in directions that are not dependent upon the difference in the type of stimulus presented to their several end organs. Such a difference must be held in mind when the hippocampus is classed with them. The pyriform lobe, on the other hand, is interpreted as an olfacto-somatic-visceral correlation center, because it receives fibers which are connected with definitely somatic and visceral systems. The simplicity and clarity of this type of reasoning may add confusion if projected into such areas as the prefrontal, whose function is more elusive than either its anatomical structure or its connections. The understanding of the last two is fundamental, however, and its lack has led to a great deal of misinterpretation when animal experimentation has been carried forward without it.

The type and orientation of the cells forming the primitive olfactory cortex, so beautifully outlined by Kappers, is suggestive, certainly, when applied to more complex cortical stratifications and allows us a concept simple enough to be grasped, and yet we know nothing in reality of the actual functioning of those interrelated cellular types. Again, it is an interesting fact that the general pallium of the alligator is related, by an afferent neurone, to an area of the corpus striatum, and this in turn to the medial and lateral nuclei of the thalamus. But this neuronic chain does not mean that the type of impulse carried is necessarily general cutaneous sensibility. Or it may be, and yet the entrance of that fiber need not be the cause for the development of a general pallium; both the fiber and general pallium appear in reptiles simultaneously. The physiological test of interruption of neuronic connections has not been applied. The functional analysis of peripheral systems and their primary nuclei in the nervous system cannot be applied to their related telencephalic centers except in lower vertebrates, and there only if we think that the activity of the telencephalon is so primitive that it cannot modify that of lower centers in any manner, whatever. In all work, and especially in that upon the cortex, it is important to separate the observed fact and its interpretation.

The presentation of the studies in the development of the human telencephalon furnishes another acute illustration of the importance of ontogenetic recapitulation; this time for problems connected with the nervous system. All the subdivisions of the primitive telencephalon are present; and although the early elaboration of the neopallium and its subsequent rapid growth might be thought of as disturbing the growth rhythms of other parts, so that they do not mature in phylogenetic order, their early differentiation follows closely the series as it is

known. The time of development of the projection areas within the neopallium is suggestive of their appearance as differentiated centers phylogenetically. The early differentiation of the pre- and postcentral gyri could be so interpreted. And from Bolton's work, the area striata, the visual association and finally, the prefrontal area follow. Not only is the sequence of differentiation of definable areas significant, but further, that of their contained laminae; the receptive layers and the motor projection layers are better developed earlier, and, although these may not reach maturity much sooner than those whose connections are mainly inter-regional, their development is always markedly ahead of the supragranular layers.

In pathological processes such as those studied by Bolton and Brouwer, not only do the cortical areas show involution in the reverse order of their evolution, but also the layers themselves. This general "law," that the first to appear embryologically or phylogenetically shall be the last to disappear or the least damaged; and the last to appear shall be the first to disappear or the most affected by pathological processes, is not confined to anatomical relationships within the nervous system. It may be seen also, in Riddoch's studies of spinal man. The same reflex, a flexion response to a noxious stimulus on the sole of the foot, was the first to be elicited and the last to be suppressed, and all the stages of its development were repeated in the reverse order when the period of gradual failure supervened. In a like manner, the later appearing extensor tendon jerk was the first to suffer. Again, it was noticed in Head's observations on aphasia, that symbols learned early in life, that is, the simplest kinds of propositional formulation, are the ones to suffer least, whereas those of higher propositional value (i.e., the more abstract) were more likely to be disordered. The effects of cortical damage are now considered, not as products of irritation, but as phenomena of release. Yet release does not yield, of necessity, an increase in activity; rather, it is often expressed as a cessation or as a difficulty in initiation. Such phenomena are especially demonstrable in lesions of the motor cortex.

Every student of the nervous system is thoroughly familiar with the projection of the parts of the body upon the motor cortex; but that familiarity should not become too fixed, since the region has a tremendous capacity for variation. The phenomena described as facilitation, reversal and deviation of response, and the slightly variable position of cortical points, are indicative of the wealth of association which exists in the stratifications of its layers. That the threshold for response to a

given stimulus is lower for the cortex itself than for the underlying fibers, and further, the fact that the amount of reaction following a cortical excitation does not entirely depend upon the size of the current, but upon the responses which have preceded it, as well, leave the impression that muscular contractions of cortical initiation are more facile and labile, more capable of modification, than those aroused at lower levels.

In the "somaesthetic" cortex there is some definite localization of parts of the body. The hand is more generously represented than any other region. But again, the types of sensation discoverable in this distal extremity suffer in diverse directions, dependent, to a certain extent, upon site of the lesion. When the precentral gyrus is superficially injured, sense of position and passive movement are impaired, together with the awareness of shape in either its two or three dimensional aspects. In lesion of the postcentral gyrus, although often point localization and the awareness of one attribute of an object, such as its smoothness or roughness, remain, nevertheless the ability to distinguish an object by "somaesthetic" knowledge is lost. Further, increased fatigue and variability of threshold are found, together with facile discouragement by wrong interpretation, all of which are never observed in the testing of individuals suffering from the "thalamic syndrome." Comparing the latter condition, which is in a certain sense also a cortical loss, with cortical lesions proper, characteristics of somaesthetic cortical function may be reduced, resembling in some respects those of activity in the motor area. Apparently intactness of this cortex lowers the threshold for stimulation; allows a finer discrimination in differences of graded stimulation, and in peripheral localization of the place stimulated; and aids in grading the response. Moreover, the interpretation lacks affective quality. With this cortex fine distinctions in peripheral stimuli can be made and held for comparison with those which have preceded or are to follow, and it confers significance on the sensory stimulus given it.

The fact that the awareness of position and passive movement is always more grossly injured than other "somaesthetic" sensibilities might be interpreted as evidence for the late phylogenetic representation in the cortex. Their injury in superficial lesions of the precentral gyrus might be correlated with the great increase of the supergranular laminae in anthropoid apes and man. Indeed, lability in the response of the motor region may be dependent upon the very existence of these layers, for the phenomena of facilitation, deviation and reversal of response were

observed in primates. It would be of interest to know to what extent the motor cortex of subprimates, where, within the limits of previous observations, the disorders resulting from cortical ablations have been explained only as defects in motor response, serves somaesthetic perception.

When the function of the occipital lobe of man is read in terms of damage to visual awareness, one point-to-point type of localization emerges, the quadrant projection of the retina upon the area striata. Injuries to other parts of this lobe may be followed by abnormal interpretation of or complete loss of the significance of objects stimulating the retina, but not by total unawareness For such lesions the attributes of objects may be differently affected, for example, the interpretation of form, of relative intensity and of color, or the concepts of the use of objects and the significance of words. Again, the peculiar difficulty with the interpretation of distance and the third dimension (found in deep lesions of the supramarginal and angular gyri), unaccompanied as it is by loss of the knowledge of form, color, shades, or by lack of appreciation of the use and significance of objects, and often attended, as it is, by disturbances in eye movements which are not paralysis, might very properly be interpreted as a loss in the appreciation of relations, or in proper interpretation of them, similar to the losses described by Head for the sensory cortex (Holmes).

The damage in aphasia might be thought of as a disintegration of the function of symbolic representation. In this process three levels are exposed: at the highest level, formulations of high propositional value, the more abstract types, take place; on the second, more automatic and simple integrations; and at the lowest level, symbolic expression of emotional states only. Although the data distribute the emphasis in the disorder in a certain relation to the localization of the cortical lesion, no plane can be drawn which cuts the difficulties analyzed into two distinct types, such as motor and sensory, or the sensory, again, into "blindness" to spoken or written words. To the extent to which the disorder is one of parts and not of function as a whole, disintegration is not along clean cut anatomical lines; rather what might be called physiological moieties are attacked. From this point of view aphasia must be studied if understanding of speech difficulties is to progress.

Just how far the loss of orientation in space seen in the lesions of the frontal lobe is related to the similar loss in the sphere of "ethics" and "morals" cannot be conjectured. But just as for the motor and somaesthetic cortices, certain aspects of intact function may be inferred by

their absence in lesion. Thus the intact frontal cortex seems to lend to purposive movements the quality of intention and to the appreciation of a group of phenomena, their comprehension as a whole. Both these qualities are essential,—the one on the motor side, the other on the sensory,—for orientation in three dimensions or in the four dimensional range of life.

Although there is apparent in the cortex no definite localization, in the old sense, of centers, nevertheless certain physiological and psychological changes have been demonstrated to occur more frequently with some sites of lesion than with others. The depth and breadth of lesion is also of importance. Certainly the cortex of man cannot be considered, in the light of recent studies, as equipotential. In its parts, the function of the human cortex cerebri seems to be one of discrimination, peripheral localization, integration and evaluation of the various peripheral excitations, and initiation of the adequate response. It gives to phenomena appreciation and significance, and relates them in space and time and, in particular, to the body in which it exists.

It is not unreasonable to consider that certain aspects of muscular control and of the peculiar ability to form associations and create meaning for phenomena have a definite substratum in the nervous tissue of the cerebral cortex. Minor variations in the functioning of this may well be in part the basis of marked variations in individuals and groups. Just how far physical environment and social restraint are able to modify the working of its innate structural relationships is not known. Nevertheless the so-called educability of an individual may be taken as an indication that the pattern of associations may be cut in a definite way, destroyed and even recut. And on the other hand, we do know that associations painfully constructed in the process of gaining experience and the pattern of discharge into lower motor centers are both capable of being markedly changed in individuals by cortical lesions, by drugs, by toxins and by great emotional pressure; that discrimination and significance, names for what appear to be characteristics of cerebral processes, which modify the activities of lower motor centers, may be lost.

We have been discussing the present status of the understanding of that tissue upon whose intactness and integrity of function depend our mores, our society, our civilization; out of whose peculiar activity grow literature, art, science; indeed those activities which, anthropomorphically speaking, differentiate us from the other animals and make us what we think we are—men.

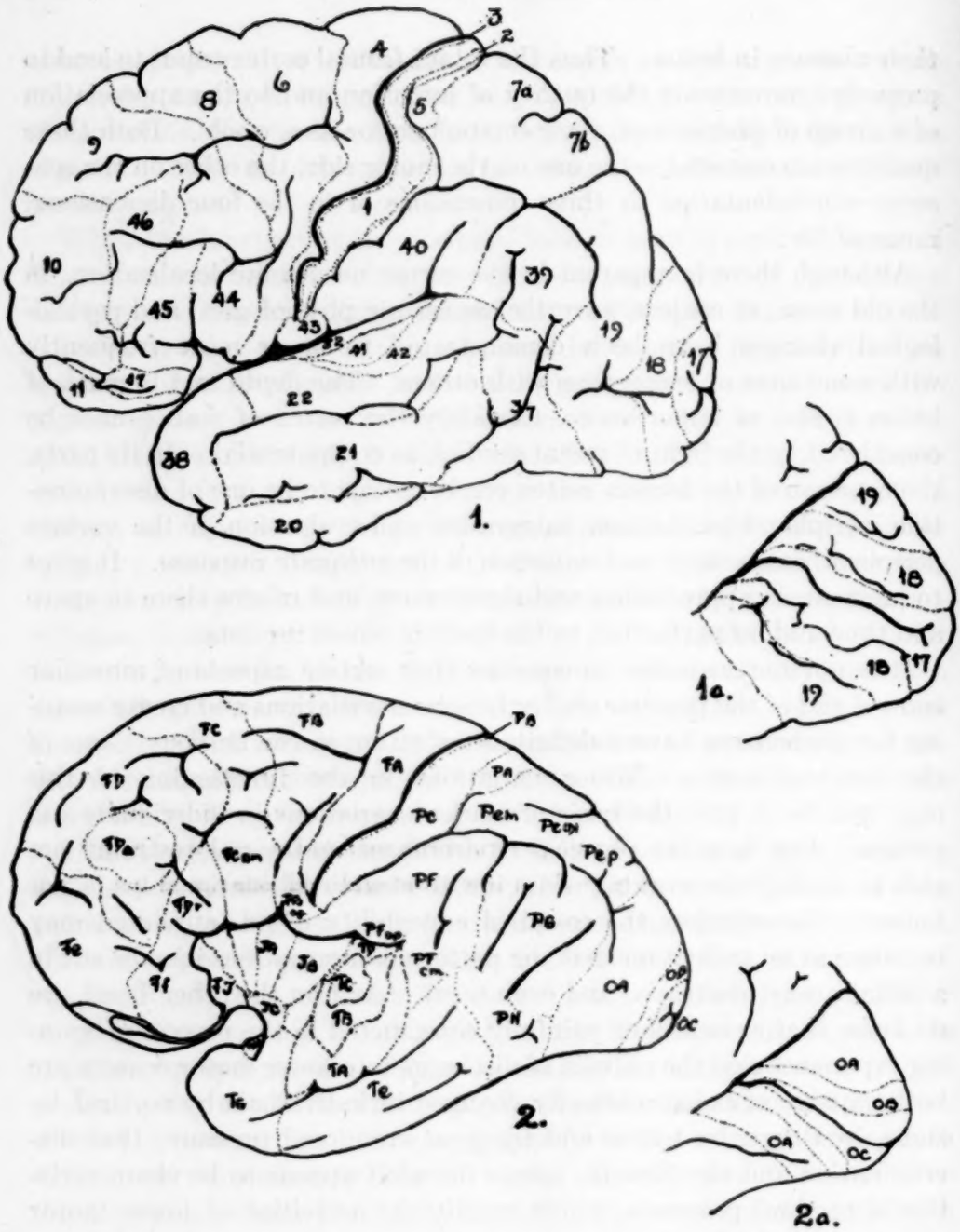

Fig. 1 and 1a. Simplified sketches of the cyto-architechtonic cortical fields projected on the lateral surface of the hemisphere and the mesial surface of the occipital lobe of man. After Brodmann (1909).

Figs. 2 and 2a. The cyto-architechtonic fields of the cerebral cortex of man; total lateral surface and mesial surface of the occipital lobe. The region of the Insula is exposed, so that the buried cortex attending all lobes is visible, particularly that contiguous to the superior temporal convolution. Simplified. After Economo and Koskinas (1925).

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